CARDIOPULMONARY, HEMODYNAMIC, AND NEUROHUMORAL RESPONSES TO ACUTE EXERCISE IN PATIENTS WITH CHRONIC HEART FAILURE

By

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A DISSERTATION PRESENTED TO THE GRADUATE SCHOOL OF THE UNIVERSITY OF FLORIDA IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE OF DOCTOR OF PHILOSOPHY

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This work is dedicated to my family for their endless love, patience, and support;

and particularly to my wife Kathy.

Charlie Mike

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The prognosis and morbidity of chronic heart failure (CHF) patients (pts) may be more closely linked with the level of neurohumoral activation and control of the circulation than with central hemodynamics. In CHF pts, resting indices may not be representative of abnormal neurohumoral responses that occur during normal daily activities or exercise (EX) rehabilitation. The temporal pattern of neurohumoral, cardiopulmonary, and hemodynamic activation during EX was evaluated in 15 CHF pts, 62.1±7.1 (mean±sd) years of age, and compared with 9 healthy age-matched controls (CON) (67.3±5.1). Data from this study identify several factors that may contribute to the EX intolerance in CHF: (1) narrowing of the cardiopulmonary reserve capacity, (2) abnormal activation of several neurohormones involved in fluid regulation and cardiocirculatory control, (3) EX-induced hemodynamic changes resulting in increased

plasma concentrations of prescribed medications, and (4) contracted plasma volume (PV) and blood volume (BV).

Exercise capacity (VO_{2peak}=15.0±3.6 ml.kg^{-1}.min^{-1}) was markedly depressed in the CHF group compared with CON (VO_{2peak}=26.3±5.8 ml.kg^{-1}.min^{-1}). The chronotropic reserve during a symptom-limited EX test was significantly less in CHF compared with CON (47.8±16.3 vs. 71.8±21.5 beats.min^{-1}). Elevated plasma angiotensin II (ANG II), vasopressin (AVP), α-atrial natriuretic peptide (α–ANP), and *B*-ANP levels indicated that, despite pharmacotherapy, many neurohormones remain hyperactivated at rest in CHF. Although there was further evidence of neurohumoral hyperactivity post-EX, EX-induced changes in plasma neurohormones were similar in magnitude between groups. With the exception of α–ANP and *B*-ANP, these data suggest that compensatory physiological adaptations and pharmacotherapy adequately regulate many of the neurohormones involved in cardiocirculatory control and fluid regulation. In both CHF and CON, EX-induced hydrostatic and oncotic pressure gradients caused an intensity-dependent decrease in PV and BV that resulted in a significant increase in plasma digitalis at the higher intensity workloads in CHF pts. Resting relative PV and BV were 34.1±12.9 vs. 44.5±9.0 ml.kg^{-1} and 58.5±12.3 vs. 70.8±12.6 ml.kg^{-1} in CHF pts and CON, respectively, suggesting that pharmacotherapy may contract PV and BV in CHF pts.

These findings demonstrate that an EX test may be useful in identifying underlying pathophysiological adaptations in CHF. Future studies are needed to determine the effect of varying pharmacotherapy regimens and long-term EX training on central cardiopulmonary, hemodynamic, and neurohumoral variables, particularly those variables associated with increased morbidity and mortality in CHF.

CHAPTER 1
INTRODUCTION

Heart failure is defined as "the pathophysiological state in which an abnormality of cardiac function is responsible for failure of the heart to pump blood at a rate commensurate with the requirements of the metabolizing tissues and/or to be able to do so only from an elevated filling pressure" (Braunwald, 1988, p.393). This definition implies that there is an alteration in the normal physiological pumping capacity of the heart. This alteration is principally due to three conditions (Braunwald, 1988): (1) a loss of cardiac muscle secondary to ischemia related to coronary artery disease (myocardial infarction), (2) a loss of myocardial function due to viral and/or primary diseases (myocarditis, endocarditis, thyrotoxicosis), and (3) cardiac decompensation secondary to poorly controlled hypertension and/or valvular disease.

Chronic heart failure (CHF) continues to be a major health problem and is the only cardiovascular disease whose incidence and prevalence are growing in the United States. The overall prevalence of CHF is estimated to be more than 3,000,000 cases resulting in approximately 400,000 fatalities annually. Of these fatalities, 35% to 45% are reported to be sudden death (Kannel et al., 1988; Parmley, 1989; Smith et al., 1988). In addition, heart failure remains a major cause of morbidity and is the most common hospital discharge diagnosis in the Medicare population (patients over 65 years of age), accounting for approximately $4.5 billion in annual expenditures (Blumenfeld & Laragh, 1994).

Medical treatment for CHF will continue to financially burden both the patients and the healthcare system as it is estimated that by the year 2030 the number of persons over 65 years of age will exceed those under 65. This will undoubtedly result in a significant increase in the number of persons diagnosed with heart failure (Ghali et al., 1990).

The treatment of CHF is generally aimed at correcting the underlying etiology and/or controlling the heart failure state (Smith et al., 1988). Numerous pharmacological agents are available which help improve central hemodynamics by reducing cardiac afterload or enhancing myocardial contractility. Additional pharmacological agents are used to reduce excessive fluid retention. Traditional CHF pharmacotherapy usually includes cardiac glycosides, ACE-inhibitors, and diuretics from which treatment many patients experience resolution of their symptoms at rest (Cohn et al., 1986; Feldman et al., 1993; Lenfant, 1994; Pepine, 1996; Remme, 1994; SOLVD Investigators, 1991, 1992; Swedberg et al., 1992). While some types of pharmacotherapy may reduce mortality, the majority have failed to translate into long-term beneficial effects and most patients continue to experience activity-related symptoms, including shortness of breath, muscle fatigue, and weakness (Drexler et al., 1992a). As a result, CHF patients often complain of chronic fatigue and are unable to perform many of their normal daily activities. Thus, despite pharmacological treatment, the clinical phase of CHF includes a marked decline in functional state, as defined by exercise tolerance and capacity with a subsequent decrease in quality of life. The decline in exercise capacity has been shown to be a significant predictor of mortality in CHF patients (Cohen-Solal & Caviezal, 1994; Cohn et al., 1988; Mancini et al., 1991; Parameshwar et al., 1992; Roul et al., 1994; Szlachcic et al., 1985).

Justification for Research

Paradoxically the degree of left ventricular dysfunction does not correlate with the clinical severity of CHF (Benge et al., 1980; Franciosa et al., 1979, 1980; McKirnan et al., 1984) suggesting that peripheral compensatory mechanisms are involved. It has been suggested that the prognosis and morbidity of the heart failure syndrome may be more closely linked with the neurohumoral control of the circulation than with ventricular function (Benge et al., 1980; Cohn, 1992; Franciosa et al., 1980; Francis et al., 1982). Several neurohormones including norepinephrine (NE), angiotensin II (ANG II), arginine vasopressin (AVP), aldosterone (ALDO), and atrial natriuretic peptide (ANP) are often elevated in the acute and chronic stages of heart failure (Benedict et al., 1993; Cohn, 1992; Francis et al., 1984; Kirlin et al., 1986; Kubo et al., 1990).

The purpose of the neurohumoral activation is to maintain arterial pressure despite the loss in myocardial function. However, two vicious cycles develop as a result of chronic neurohumoral hyperactivation: (1) vasoconstriction, and (2) renal sodium and water retention. By increasing systemic vascular resistance and ventricular afterload, chronic vasoconstriction ultimately contributes to myocardial hypertrophy in many patients. Renal sodium and water retention increase circulating blood volume which results in increased ventricular filling pressure and diastolic wall stress. Together, these cycles eventually lead to progressive myocardial and vascular dysfunction, hypervolemia and edema, peripheral tissue (e.g. skeletal muscle) abnormalities, and finally the clinical state of heart failure (Remme, 1994).

Although neurohumoral hyperactivity may normalize with pharmacotherapy-induced restoration of cardiovascular homeostasis (Dzau et al., 1981; Watkins et al., 1976), several studies indicate that CHF patients may continue to have an abnormal autonomic response to dynamic exercise (Chidsey et al., 1962; Francis et al., 1982b; Kirlin et al., 1986). Interestingly, the temporal pattern of many neurohumoral responses occurring during the transition from rest to steady-state and non-steady-state exercise have not been well established. The primary purpose of this study is to determine the temporal pattern of neurohumoral activation during graded exercise in CHF patients. Recognizing the increasing prevalence of exercise rehabilitation being prescribed as a therapeutic modality for CHF patients, the potential for abnormal neurohumoral activation during graded exercise warrants further investigation.

A second purpose of the proposed research is to determine the temporal pattern of plasma volume shifts occurring during the transition from rest to exercise. Recognizing that standard CHF pharmacotherapy includes cardiac glycosides (e.g. digitalis) and anticoagulants (e.g. coumadin, warfarin) which have narrow dose-response therapeutic limits, exercise-induced plasma volume shifts could substantially increase intravascular drug concentrations and potentially increase the risk of pharmacotherapy-induced morbidity (e.g. cardiac arrhythmias, hemorrhaging).

Purpose of the Study

Thus, there are four critical questions to be addressed regarding the etiology of the diminished exercise capacity observed in most CHF patients: (1) Do CHF patients exhibit

an altered cardiopulmonary response to graded exercise?, (2) Does plasma volume shift from the intravascular to the extravascular compartment in an intensity-dependent manner during graded exercise in CHF patients?, and if so, does the plasma concentrations of prescribed medications change during exercise?, (3) Do CHF patients demonstrate an altered neurohumoral response during graded exercise? (4) Does standard pharmacotherapy adequately restore blood volume to normal levels in CHF patients?

The present study is designed to investigate the effects of acute submaximal and maximal exercise on cardiopulmonary, hemodynamic, and neurohumoral responses in patients with CHF. The specific aims of the proposed study are to determine the effects of submaximal and maximal treadmill exercise on: (1) cardiopulmonary variables including heart rate, blood pressure, oxygen consumption, carbon dioxide production, minute ventilation, and oxygen saturation; (2) intra- to extravascular plasma volume shifts and the hemoconcentration of circulating drugs (e.g. digitalis glycosides); and (3) neurohormones including angiotensin II (ANG II), arginine vasopressin (AVP), aldosterone (ALDO), α-atrial natriuretic peptide (α-ANP), and *B*-atrial natriuretic peptide (*B*-ANP). In addition, a fourth aim of the proposed study is to determine plasma and blood volumes following standard diuretic and ACE-inhibitor therapy.

Research Hypotheses

The principal hypotheses of the research protocol aimed at evaluating the acute exercise responses in patients with CHF secondary to ischemic heart disease (compared to healthy subjects) are as follows:

(1) In contrast to normal resting levels, cardiopulmonary variables will be markedly blunted in the CHF patients during submaximal and maximal treadmill exercise;

(2) Graded exercise will result in an intensity-dependent plasma volume shift and an increase in the plasma concentration of prescribed medications;

(3) In contrast to normal resting levels, vasoconstrictor and fluid regulating neurohormones will be markedly hyperactivated during graded exercise in CHF patients;

(4) The inactive subtype, *B*-ANP, will account for a greater proportion of the total circulating ANP at rest and released in response to graded exercise in CHF patients; and

(5) Blood volume will remain significantly elevated at rest despite standard pharmacotherapy in CHF patients.

Delimitations

This study is delimited to the following:

(1) Fifteen volunteer patients with heart failure secondary to ischemic heart disease, based on documented myocardial infarction, and/or cardiac catheterization;

(2) Patients with a New York Heart Association (NYHA) classification of II or III, and without significant other disease or contraindications to exercise;

(3) Ten healthy, non-athletic and non-medicated subjects that match the CHF patients with respect to gender, age, and body size;

(4) Patients / subjects ranging in age from 18 to 80 years;

(5) Patients with a minimal duration of heart failure of no less than 4 months;

(6) Patients consenting not to alter diet or physical activity habits during the study; and

(7) Patients without cardiac pacemakers or internal defibrillators.

Limitations

This study is limited by the following:

(1) Patients received numerous pharmacological agents which may influence cardiopulmonary, hemodynamic, and neurohumoral responses to exercise;

(2) Patients did not all receive the same pharmacological agents or respective dose;

(3) The duration of heart failure among patients varied which may influence the cardiopulmonary, hemodynamic, and neurohumoral responses to exercise;

(4) The severity of heart failure among patients was not the same and may influence the responses to exercise.

Significance of Research

Recognizing that plasma neurohormone concentrations are closely related to morbidity and exercise capacity, which in itself is a powerful independent predictor of survival, supervised exercise testing may be essential in unmasking neurohumoral hyperactivity in CHF patients with normal resting indices. Such information may help physicians develop more appropriate treatment strategies for patients with heart failure. Furthermore, considering that exercise training has been shown to buffer neuroendocrine hyperactivity, this research could form the background necessary for designing an multiple intervention study incorporating exercise rehabilitation and pharmacotherapy.

CHAPTER 2
REVIEW OF LITERATURE

The Heart Failure Syndrome

Heart failure has been defined as "the pathophysiological state in which an abnormality of cardiac function is responsible for failure of the heart to pump blood at a rate commensurate with the requirements of the metabolizing tissues and/or to be able to do so only from an elevated filling pressure" (Braunwald, 1988, p.393). This decrease in ventricular function and subsequently cardiac output is principally due to three conditions (Braunwald, 1988): (1) a loss of cardiac muscle secondary to coronary artery disease (i.e. myocardial infarction), (2) a loss of myocardial function due to viral and/or other primary diseases (i.e. myocarditis, endocarditis, thyrotoxicosis), and (3) cardiac decompensation secondary to poorly controlled hypertension and/or valvular disease. The overall prevalence of CHF in the United States is estimated to be more than 3,000,000 cases resulting in approximately 400,000 fatalities annually. Of these fatalities, 35% to 45% are reported to be sudden death (Kannel et al., 1988; Parmley, 1989; Smith et al., 1988).

The treatment for CHF is generally directed at correcting the underlying etiology and/or controlling the heart failure state. Traditional management of CHF includes a pharmacotherapy package composed of cardiac glycosides, ACE-inhibitors, and diuretics prescribed to relieve the clinical symptoms. Although some types of pharmacotherapy

(Drexler et al., 1991b). Many patients experience resolution of their symptoms at rest, but most continue to experience activity-related symptoms and are often unable to perform many of the normal activities of daily living. As a result, the clinical phase of CHF includes a marked decline in functional state, as defined by exercise tolerance and capacity with a subsequent decrease in quality of life. A decline in exercise capacity has been shown to be a powerful predictor of survival in CHF patients (Szlachcic et al., 1985).

Several investigators have clearly shown that the degree of left ventricular dysfunction (LVD) does not correlate with the clinical severity of CHF (Benge et al., 1980; Franciosa et al., 1979, 1980; McKirnan et al., 1984). This suggests that, in addition to adaptations influencing central hemodynamics, peripheral compensatory mechanisms must be involved. The reduction in myocardial function is countered with several compensatory adaptations designed to maintain perfusion pressure to the vital organs. These compensatory adaptations include: (1) increased end-diastolic volume (ventricular dilatation), (2) sympathetic nervous system-induced vasoconstriction, (3) neurohumoral-induced vasoconstriction and renal sodium and water retention, (4) myocardial hypertrophy, (5) impaired vasodilatory capacity; and (6) intrinsic alterations in skeletal muscle. Although these adaptations may be effective in maintaining adequate perfusion pressure under resting conditions, the capacity to sustain cardiac performance during exercise is reduced. Unfortunately, these compensatory adaptations ultimately contribute to the pathogenesis of the heart failure syndrome.

Under normal circumstances, cardiac and arterial mechanoreceptors exert a tonic inhibitory influence on sympathetic nervous activity to the heart and peripheral circulation as well as exerting a restraining influence on the circulating levels of pressor hormones

as well as exerting a restraining influence on the circulating levels of pressor hormones such as NE, epinephrine (EPI), AVP, and the renin-angiotensin-aldosterone system (RAAS) (Cowley et al., 1984). These neurohumoral systems are involved in electrolyte balance and blood pressure homeostasis and are responsible for maintaining arterial pressure and peripheral perfusion. It is not surprising that several neurohormones including NE, EPI, ANG II, ALDO, AVP, and ANP are elevated in the acute and chronic stages of CHF (Cohn et al., 1984; Drexler et al., 1991a; Francis et al., 1984; Kirlin et al., 1986). These systems rapidly respond as a multifaceted defense against dehydration and traumatic hemorrhage in healthy individuals, however, attempts to maintain perfusion pressure by increasing peripheral vascular resistance and retaining intrarenal sodium and water in CHF patients may have adverse consequences on the already impaired ventricular function and congested circulation. Although many of the neurohumoral abnormalities may normalize with restoration of cardiovascular homeostasis (Dzau et al., 1981; Watkins et al., 1976), several studies indicate that patients with CHF may have an abnormal autonomic response to dynamic exercise (Chidsey et al., 1962; Francis et al., 1982; Kirlin et al., 1986). Interestingly, the temporal pattern of many neurohumoral responses and/or interactions with cardiac hemodynamics occurring during the transition from rest to exercise have not been well established.

Neurohumoral Activation

The heart failure syndrome is characterized not only by impaired ventricular function and sympathetic discharge, but also by an increase in endogenous vasoconstrictor

substances including NE, ANG II, AVP, and endothelin (Benedict et al., 1993; Cohn, 1992; Drexler et al., 1991b; Francis et al., 1984; Kirlin et al., 1986; Krum et al., 1995). The purpose of the neurohumoral activation is to maintain arterial pressure despite a loss in myocardial function. However, as a result of chronic neurohumoral activation two vicious cycles develop: (1) vasoconstriction, and (2) renal sodium and water retention. Arterial vasoconstriction increases systemic vascular resistance and afterload and ultimately contributes to myocardial hypertrophy. Renal sodium and water retention increase circulating blood volume which results in increased ventricular filling pressure and diastolic wall stress. Together, these vicious cycles may eventually lead to progressive myocardial and vascular dysfunction, hypervolemia and edema, peripheral tissue abnormalities, and finally the clinical state of heart failure (Remme, 1994).

Sympatho-Adrenal Activation

Sympathetic reflexes rapidly compensate for acute myocardial failure to maintain cardiac output compatible with survival. Within seconds of a reduction in stroke volume and arterial pressure, a baroreceptor-sympathetic-mediated increase in venous return and inotropic state induce ventricular dilation and increase myocardial contractility (Guyton, 1996; Porter et al., 1990; Ross, 1976). Although normal resting cardiac output (5 L/min) is restored concomitant with an increase in right atrial pressure (+6 mmHg), the sympathetic-mediated increase in circulating catecholamines (NE, EPI) remains elevated into the chronic stages of heart failure (Benedict et al., 1993; Cohn et al., 1984; Francis et al., 1990). Unfortunately, the potential adverse effects of chronic sympathetic activation on cardiac muscle, the kidneys, and the vasculature are numerous and contribute to the

clinical manifestations (Floras, 1993). Plasma concentrations of NE and EPI are indexes of sympatho-adrenal activity and, despite standard pharmacotherapy, are usually two to three times higher at rest in patients with CHF when compared to healthy age-matched subjects. The magnitude of elevation of plasma NE is related to the degree of left ventricular dysfunction and carries an ominous prognosis (Cleland et al., 1987; Cohn et al., 1984). Although plasma NE concentrations normally increase with age at a rate of approximately 13% per decade (Hoeldtke & Cilmi, 1985), mean arterial plasma NE concentrations are approximately 600 pg/ml in CHF patients compared to 200 pg/ml in healthy age-matched adults (Francis et al., 1982a, 1985; Hasking et al., 1986; Kirlin et al., 1986). Increased spillover of NE and impaired clearance contribute to the elevated plasma levels of NE in both CHF patients and the healthy elderly (Davis et al., 1988; Hasking et al., 1986). An important distinction between the normal physiological processes associated with aging and the pathophysiology associated with the heart failure syndrome is that, in CHF, sympathetic activity is distributed non-uniformly with significant increases to the heart and kidneys but normal activity to other target organs such as the lungs (Floras, 1993). Increased renal sympathetic activity contributes significantly to the altered hemodynamics, sodium and water retention, and modulates the actions of other vasoactive hormones (i.e. ANG II, ALDO) (Floras, 1993; Francis et al., 1984). The direct and indirect effects of augmented sympathetic activity are largely responsible for the changes in regional blood flow at rest and the maldistribution of blood flow that occurs during dynamic exercise in CHF patients (Hasking et al., 1986; Zelis et al., 1975).

Arterial and cardiopulmonary baroreceptor dysfunction is commonly observed in CHF and is believed to contribute to the disordered sympathetic-mediated elevation in

plasma NE and other pressor hormones (Dibner-Dunlap & Thames, 1992; Ferguson et al., 1992; Porter et al., 1990; Thames et al., 1993). Under normal conditions, unloading of the baroreceptors by lowering blood pressure increases sympathetic discharge and modulates the withdrawal of vagal inhibition of the heart. This response defends blood pressure through both positive inotropic and chronotropic mechanisms and induces systemic vasoconstriction which increases total peripheral resistance thereby increasing afterload and improving venous return. However, chronic activation and/or resetting of the baroreceptors in response to rapid fluctuations in blood volume and transmural pressure often results in baroreceptor desensitization and thus, abnormal baroreceptor-mediated activity. Several mechanisms have been postulated to induce this abnormal response including structural and/or biochemical abnormalities of the baroreceptors, altered compliance of the vascular structures containing the mechanosensory nerve endings, abnormal central nervous system processing of afferent impulses, and/or impaired peripheral responses to the efferent signal (Thames et al., 1993). Regardless of the etiology, the reduction in baroreceptor sensitivity may be partially responsible for augmenting the elevated basal NE levels as well as attenuating sympatho-adrenal activity during high-intensity exercise in CHF patients (Francis et al., 1982a, 1982b; 1985).

In both healthy persons and CHF patients, dynamic exercise elicits an intensity-dependent and pronounced activation of the sympatho-adrenal system (Christensen & Galbo, 1983; Galbo et al., 1975). During exercise, sympatho-adrenal activation induces systemic vasoconstriction both directly (via vascular alpha receptors) and indirectly (via renin-mediated ANG II formation) which enhances venous return and shunts blood away from nonexercising tissue in order to maintain adequate perfusion pressure in active

skeletal muscle tissue (Zelis et al., 1975). Plasma NE levels increase gradually with increasing intensities until approximately 50-70% of VO_{2peak} at which point they increase markedly in a curvilinear fashion reaching an apex at peak exercise (Francis et al., 1982a, 1982b). The increase in plasma catecholamines and other hormone concentrations is believed to be partially caused by increasing splanchnic and renal vasoconstriction (Tidgren et al., 1991). Interestingly, the temporal kinetics of NE appearance appears to be different in patients with CHF. Norepinephrine increases to a greater extent at lower levels of exercise in CHF patients but does not reach the extremely high levels during maximal exercise as seen in healthy persons (Adamopoulos & Coats, 1990; Francis et al., 1982a, 1982b, 1985; Wilson et al., 1989). Although exercise-induced sympatho-adrenal activation is beneficial in healthy persons, the same response may have a deleterious effect on the circulation in heart failure. Sympathetic discharge and parasympathetic withdrawal to the heart may augment stroke volume by its positive inotropic effect, but sympathetic induced peripheral vasoconstriction might impair stroke volume by raising impedance to left ventricular ejection. Thus, the higher plasma NE levels in CHF patients at low work loads could be helping support cardiac function or could be contributing to exercise intolerance. Additional studies are needed to determine the interaction between increases in plasma catecholamines, cardiac output, and total peripheral resistance during graded exercise. Furthermore, there appears to be a lack of studies in the existing literature quantifying the relationship between exercise-induced plasma volume kinetics and NE concentrations.

The Renin-Angiotensin-Aldosterone System

In conjunction with sympatho-adrenal system activation, the RAAS increases preload and afterload secondary to systemic vasoconstriction and renal sodium and water retention. Although the role of the RAAS in heart failure is not completely understood, plasma concentrations of renin (PRA), ANG II, and ALDO have been shown to be markedly elevated in many patients with CHF (Benedict et al., 1993; Francis, et al., 1984; 1990). Fortunately for many patients, elevated plasma concentrations of RAAS hormones normalize with pharmacotherapy (Dzau et al., 1981).

Several mechanisms are known to stimulate the RAAS by promoting the secretion of renin from the juxtaglomerular complex and vascular endothelium: (1) increased sympathetic stimulation of), *B*-adrenergic receptors located on the renin secreting cells, (2) increased circulating catecholamines, (3) decreased renal perfusion pressure, (4) alterations in the sodium load presented to the macula densa, and/or (5) a combination of all the above (Hirsch et al., 1987; Morali et al., 1991). Chronic RAAS stimulation often results in a "permanent" increase in vasomotor tone which may contribute to vascular wall hypertrophy and neurogenic vasoconstriction (Daly & Sole, 1990; Zelis & Flaim, 1982). Furthermore, the increase in plasma volume (secondary to ANG II- and ALDO-induced sodium and water retention) increases myocardial preload by stretching the sarcomeres to a more optimal length, thereby facilitating cardiac output which leads to the development of myocardial hypertrophy.

Production of the pressor hormone ANG II is controlled by two enzymatic steps: (1) the reaction of renin on its substrate, angiotensinogen, which is the rate-limiting step generating angiotensin I (ANG I), and (2) the proteolytic cleavage of ANG I into ANG II

by the angiotensin-converting enzyme (ACE) (Guyton, 1996). Renin is primarily synthesized and secreted into the blood by the juxtaglomerular cells located in the macula densa in the afferent arterioles of the glomeruli. Although renin is not a vasoactive substance, it acts on angiotensinogen to release a 10-amino acid peptide, ANG I. Within a few seconds following the formation of ANG I, two additional amino acids are split to form an 8-amino acid peptide which is catalyzed by ACE to form ANG II (Guyton, 1996). Due to the short half-life of ANG I, PRA is often used as a marker of plasma concentrations of ANG I. Resting values for PRA in healthy adults are often not significantly different from those of CHF patients and usually range from .5-2 ng/ml per hour (Benedict et al., 1993). While the PRA profile for many CHF patients may be relatively normal, other patients often exhibit levels as high as 15 ng/ml per hour at rest (Benedict et al., 1993; Curtiss et al., 1978; Francis et al., 1984; Nicholls et al., 1992). Although ANG I has vasoactive properties, ANG II has a longer circulating half-life (approximately 1 minute) and is the effector peptide which modulates several functions including increasing peripheral vascular resistance through vasoconstriction, enhancing renal sodium reabsorption, facilitating catecholamine release from sympathetic nerve endings, and stimulating mineralocorticoid production (i.e. ALDO) in the adrenal gland. Additionally, ANG II has been implicated as a growth factor in the cardiovascular system (Paul et al., 1994). Resting values for plasma ANG II concentrations in healthy adults are approximately 2 pg/ml compared to 6-9 pg/ml for patients with compensated heart failure (Aldigier et al., 1991).

In addition to the vasoconstrictor and mitogenic properties, ANG II stimulates the production of the ALDO by the zona glomerulosa region of the adrenal cortex (Guyton,

1996). In CHF, the hypersecretion of ALDO, working in conjunction with AVP, promotes excessive sodium and water retention in the renal distal tubules and significantly contributes to the characteristic congestive, edematous state. Nicholls et al. (1992) reported resting plasma ALDO concentrations of 340 ng/l in CHF patients compared to 89 ng/l in healthy control subjects. At peak exercise, plasma concentrations of ALDO increased to 521 and 294 ng/l in CHF patients and healthy controls, respectively.

Recognizing that the RAAS is markedly activated in heart failure, several investigators have evaluated the role of ACE-inhibitors as a pharmacological treatment strategy. Results from subsequent clinical trials have concluded that morbidity and mortality can be reduced by administration of ACE-inhibitors (The SOLVD Investigators, 1991, 1992; Swedberg et al., 1992). Based on the results of these studies, standard CHF pharmacotherapy currently includes the use of ACE-inhibitors (i.e. captopril, enalapril) designed to block the conversion of ANG I to ANG II on the premise that the prevention of ANG II formation will unload the heart by reducing blood pressure and renal sodium and water retention (Gavras et al., 1978). The precise mechanism of action of ACE-inhibitors is still not completely understood. In addition to inhibiting ANG II formation, ACE-inhibitors may reduce afterload and myocardial work due to its actions on neurohumoral or vasoactive substances other than the RAAS (i.e. bradykinin), or through some specific action modulated via myocardial and/or vascular receptors (i.e. CGMP dependent pathway). In any case, the recent indication that ACE-inhibition can reverse structural vascular alterations is promising. Interestingly, acute inhibition of ACE does not improve blood flow to skeletal muscle and subsequently leg muscle perfusion and exercise tolerance remain unchanged (Drexler et al., 1987, 1989; Wilson & Ferraro,

1985). In contrast, long-term ACE-inhibitor therapy does improve regional blood flow and exercise tolerance in patients with CHF (Drexler et al., 1989). Although treatment with ACE-inhibitors may reduce resting levels of plasma ANG II and ALDO in patients with CHF (Cleland et al., 1985; Swedberg et al., 1990), the results from studies evaluating the effects of ACE-inhibitors on the RAAS and circulating catecholamines during exercise have not been consistent (Aldigier et al., 1993; McGrath & Arnold, 1986; Sigurdsson et al., 1994; Wade et al., 1987), and further research is clearly warranted. Recent studies by Sigurdsson et al. (1994) and Aldigier et al. (1993) concluded that, despite ACE-inhibitor therapy, plasma ANG II concentrations continue to increase with exercise. The mechanism(s) facilitating the exercise-induced increase in plasma ANG II concentrations remains elusive.

Exercise produces significant elevations in the neurohormones involved in fluid regulation and the increase in PRA, ANG II, and ALDO with graded exercise in healthy adults is well established (Convertino et al., 1983; Hartley et al., 1972; Kotchen et al., 1971; Staessen et al., 1987). Exercise at work levels greater that 40% VO_{2peak} stimulates an intensity-dependent secretion of renin into the circulatory system in healthy individuals, increasing markedly in a curvilinear manner at intensities greater than 70% VO_{2peak} (Kotchen et al., 1971; Staessen et al., 1987). While PRA baseline values for healthy individuals are generally in the range of 1-2 ng/ml per hour increasing up to 16 ng/ml per hour during high intensity exercise, the magnitude of increase varies significantly within the existing literature (Convertino et al., 1983; Kotchen et al., 1971; Staessen et al., 1987). The discrepancies between the findings of these studies is most likely due to differences in exercise modalities, body position, end-point work levels, and/or

consideration of the effect of exercise-induced plasma volume shifts on hormone concentrations. In similar studies assessing PRA activation, Wilson et al. (1989) and Kirlin et al. (1986) reported that PRA is markedly higher during exercise in CHF patients, reaching values at peak exercise as high as 44.5±13.3 pg/ml per hr. In CHF patients, it is speculated that the marked increase in PRA and subsequent ANG II activity augments systemic vascular resistance in an attempt to maintain blood flow to the weakened myocardium, despite significant exercise-induced shunting of blood to active skeletal muscle vascular beds. Whether plasma ANG II and/or ALDO concentrations increase in a similar manner to PRA during acute exercise in CHF patients remains to be determined.

Arginine Vasopressin

The antidiuretic hormone, arginine vasopressin (AVP), is a nine amino acid polypeptide released by the posterior pituitary with its primary action to induce antidiuresis (Guyton, 1996). Injecting concentrations as small as 2 ng have been shown to markedly increase the permeability of the collecting ducts and renal tubules thereby facilitating the reabsorption of water (Cowley et al., 1984). The precise mechanism by which AVP acts on the collecting ducts to increase permeability is only partially known, although its ability to induce structural changes in the apical wall facilitating fluid diffusion contributes substantially. Arginine vasopressin is secreted in response to changes in plasma osmolality sensed by hypothalamic osmoreceptors and has a circulating half-life of approximately 15-20 minutes. Mechanoreceptors located in the myocardial wall, particularly in the right atrium, also influence AVP secretion. When excited, these receptors send signals to the brain to inhibit AVP secretion. Conversely, AVP secretion is

stimulated when there is a fall in right atrial pressure (volume), similar to which occurs during the acute stage of heart failure. In addition to the atrial stretch receptors, decreased stretch of the baroreceptors of the carotid, aortic, and pulmonary regions also participate in increasing AVP secretion. Arginine vasopressin secreted in response to dehydration, hemorrhage, or hyperosmolality has a potent vasopressor effect. Interestingly, AVP has been shown to have a more pronounced pressor action in animals with baroreceptor denervation, sympathectomy, and nephrectomy (Cowley et al., 1984). A secondary consequence of excessive fluid retention due to AVP is hyponatremia, a common manifestation of severe heart failure that occurs when water is retained in excess of sodium. It has been shown to be a powerful independent predictor of cardiovascular mortality (Lee & Packer, 1986; Levine et al., 1982).

Several studies have indicated that plasma AVP concentrations are often, but not always, elevated in CHF (Benedict et al., 1993; Creager et al., 1986; Goldsmith et al., 1983). Data from the SOLVD Trial presented by Benedict et al. (1993) indicates that resting values for CHF patients range from 1.7 to 3.1 (median 2.4) pg/ml which is significantly higher than for healthy normal individuals who had resting plasma AVP concentrations ranging from 1.4 to 2.4 (median 1.8) pg/ml. The mechanism for the chronic release of AVP in heart failure is not well understood but is believed to be due to non-osmotic causes. As described previously, AVP secretion is associated with reductions in stroke volume and cardiac output, mediated via cardiac and arterial mechanoreceptors (Goldsmith et al., 1983; Sztalowicz et al., 1981). Some investigators have speculated that atrial stretch receptors become desensitized with CHF in a similar fashion as arterial baroreceptors, and the reduction in afferent signals normally inhibiting AVP secretion

contributes to the elevation of circulating AVP (Cowley et al., 1984; Greenberg et al., 1973; Riegger et al., 1982). This may explain, in part, the elevated plasma AVP concentrations in volume expanded CHF patients with elevated right atrial pressures. Interestingly, reducing RAAS-mediated afterload with ACE-inhibitors decreases AVP levels and subsequently enhances diuresis. Although plasma AVP levels in CHF patients do not appear to correlate with any specific cardiopulmonary variable (i.e. heart rate, mean arterial pressure, right atrial pressure, left ventricular filling pressure), serum sodium, or plasma NE, there is a modest correlation ($r=0.53$, $p<0.02$) with increases in PRA (Goldsmith et al., 1983).

Considering that AVP secretion is stimulated by changes in osmolality, plasma volume, and sympathetic drive, all of which are normal physiological responses to exercise, it is not surprising that several studies have investigated the effect of graded exercise on plasma AVP concentrations in healthy adults (Convertino et al., 1980, 1981, 1983; Wade & Claybaugh, 1980). It is surprising, however, that there are very few studies evaluating the same response in CHF patients, especially considering that a substantial number of patients have elevated plasma AVP concentrations and the fact that there is an increasing prevalence of patients enrolling in exercise programs as part of their rehabilitation process (Kirlin et al., 1986). In a series of studies evaluating young healthy subjects, Convertino et al. investigated the interrelationships of plasma volume, osmolality, AVP, and PRA to graded workloads in an acute bout of cycle ergometer exercise (1981) and following a training period (1980, 1983). The results from the acute exercise study indicate that the loss of plasma volume from the vascular space and the increased osmolality induced by increasing exercise intensities were associated with proportional

increases in plasma AVP and PRA (Convertino et al., 1981). The subsequent study demonstrated that a threshold of 50% VO_{2peak} is required to increase AVP and PRA concentrations which continue to increase in a intensity-dependent curvilinear fashion (Convertino et al., 1983). A similar study by Wade et al. (1980) also concluded that PRA and plasma AVP are linearly correlated and increase during graded exercise in an intensity-dependent fashion. Unfortunately, the data is not available to conclude that CHF patients experience a similar increase in plasma AVP concentration with graded exercise. There appears to be only one study in the existing literature which has evaluated the effect of exercise on plasma AVP in CHF patients (Kirlin et al., 1986). Kirlin et al (1986) compared PRA and AVP responses to two cycle ergometer workloads (50W, 100W). Plasma renin activity almost doubled (from 4.7 to 8.4 ng/ml per hour) during dynamic exercise in CHF patients compared with only minimal changes in the healthy subjects. Plasma AVP concentrations did not change significantly in patients with CHF (3.5 to 4.0 pg/ml), but rose in healthy subjects from resting levels (0.5 pg/ml) to levels comparable to the resting levels of the CHF group (2.0 pg/ml) (Kirlin et al., 1986). The results suggest that CHF produces substantially different patterns of neurohumoral activation during dynamic exercise compared with those of healthy persons. Interestingly, neither plasma EPI nor NE increased with exercise in the CHF patients which is in contrast to the findings of several other studies (Christensen & Galbo, 1983; Francis et al., 1982a, 1982b, 1985; Galbo et al., 1975). Considering the apparent inconsistancies in measured catecholamine concentrations and that the literature concerning AVP concentrations in response to exercise is limited, additional studies need to be conducted to verify the results of the study by Kirlin et al. (1986).

Recognizing the detrimental clinical manifestations associated with AVP-mediated actions and that plasma AVP is elevated in a significant number of CHF patients, the potential role of AVP-antagonist pharmacotherapy has been investigated (Creager et al., 1986; Gavras et al., 1984). Creager et al. (1986) demonstrated that an AVP V1 antagonist can reduce systemic vascular resistance is patients whose resting plasma AVP concentrations were greater than 4.0 pg/ml. The authors concluded that, in addition to sympathetic nervous system-induced vasoconstriction, AVP and the RAAS each contribute to systemic vasoconstriction in some patients with CHF (Creager et al., 1986). More recent studies have indicated AVP is not a primary mechanism for the increased systemic vascular resistance in most CHF patients because of the lack of relationship between AVP and increasing left ventricular dysfunction (Benedict et al., 1993). On the other hand, with ACE-inhibitor therapy as a precedent, it is possible that pharmacotherapy targeted at AVP-mediated vasoconstriction might be an additional step in the design of vasodilator therapy for CHF patients with chronically elevated plasma AVP concentrations (Goldsmith et al., 1986).

Atrial Natriuretic Peptides

Atrial natriuretic peptide (ANP) refers to a family of polypeptide hormones secreted primarily by the cardiac atria in response to distension and have potent effects on renal sodium and water handling and on systemic hemodynamics. Recent studies have determined that there are at least two similarly structured natriuretic peptides; the biologically active form α-atrial natriuretic peptide (α-ANP), and the less biologically active *B*-atrial natriuretic peptide (*B* -ANP) (Saguwara et al., 1988). Two additional

structurally-related peptides have been identified, brain natriuretic peptide (BNP) and C-type natriuretic peptide. Brain natriuretic peptide is of cardiac origin and is believed to function in concert with ANP as a dual natriuretic peptide system (Mukoyama et al., 1991). C-type natriuretic peptide is synthesized in the vascular endothelium and functions as a paracrine factor in the control of vascular tone (Clavell et al., 1993; Stingo et al., 1992a, 1992b). The normal plasma concentration of ANP is in the range of 30 pg/ml with a release rate of 2-3 ng/kg per minute and a plasma half-life of several minutes. Several studies have demonstrated that ANP possesses unique biologic actions that include natriuretic, vasodilator, renin- and aldosterone-inhibiting and antimitogenic actions (Brandt et al., 1993; Goetz, 1988; Lee et al., 1989; Margulies et al., 1991). The ultimate action of ANP is to decrease plasma volume which is accomplished primarily through its natriuretic and diuretic properties. In addition, ANP acts on the vascular endothelium via a cyclic-GMP receptor-mediated mechanism to facilitate fluid transfer into the extravascular compartments (i.e. interstitial space) (Goetz, 1988). This raises the possibility that ANP may contribute to edema formation, a clinical hallmark of CHF.

Heart failure is characterized by increased cardiac volume and pressure overload secondary to increased renal sodium and water retention and systemic vasoconstriction. Many of these hallmarks of CHF are associated with the increased activation of systemic neurohumoral and local autocrine and paracrine mechanisms (i.e. ANP). Accordingly, circulating ANP levels are significantly increased in patients with CHF and ANP has emerged as an important diagnostic and prognostic serum marker (Brandt et al., 1993; Burnett et al., 1986). Data from the SOLVD Trial reported resting values for plasma ANP in healthy adults from 31 to 64 (median value 48) pg/ml versus 54 to 225 (median

value 114) pg/ml for patients with CHF (Benedict et al, 1993). In the acute stages of heart failure, ANP may play a key role in preserving the compensated state of asymptomatic left ventricular dysfunction (Brandt et al., 1993). Evidence indicates that during this early stage ANP assists in maintaining cardiorenal homeostasis, contributes to the maintenance of sodium and water balance, and inhibits RAAS activation (Lee et al., 1989; Margulies et al., 1991). Based on these results, ANP could be an important counter-regulatory hormone reducing the deleterious effects induced by the RAAS and sympathetic nervous system. In acute heart failure the increased levels of ANP are secondary to an increase in release of stored ANP. In chronic heart failure, however, ANP elevation is secondary to enhanced cardiac synthesis and release, which are activated by the chronically increased cardiac volume and pressure overload (Perrella et al., 1992). Interestingly, Wei et al. (1993) reported that the less biologically active *B*-ANP accounts for a progressively increasing portion of the total elevated ANP in the chronic stages of heart failure. The impaired capacity to release the active form, α-ANP, may be the result of the chronic volume and pressure overload and subsequent inability of the atria to meet the demand of the system (Volpe et al., 1991). Consequently, despite the increases in circulating ANP during the chronic stages of heart failure, the kidneys continue to retain sodium and water and become hyporesponsive to endogenous or exogenous ANP (Burnett et al., 1986; Raine et al., 1986). The mechanisms for the ANP hyporesponsiveness are thought to be multifactorial and include: (1) a reduction in renal perfusion (Redfield et al., 1989), (2) increased renal sympathetic nerve activity (Morgan et al., 1989), (3) increased circulating catecholamines (McMurray et al., 1989), (4) reduced ANP binding and/or receptor downregulation (Schiffrin, 1988), (5) enhanced ANP

enzymatic degradation (Cavero, 1990), and/or (6) overwhelming activity of the RAAS (Showalter et al., 1988). Thus, a relative deficiency and/or impaired release of α-ANP or diminished response to contributes to the pathophysiology of renal sodium and water retention and systemic vasoconstriction in patients with CHF (Brandt et al., 1993).

Several studies have demonstrated that ANP correlates with the functional class of patients, PRA, plasma NE concentrations, and mortality (Davis et al., 1992; Gottlieb et al., 1989). As a result, ANP has emerged as an important diagnostic and prognostic marker in heart failure. Using a Kaplan-Meier analysis of cumulative rates of survival in patients with heart failure stratified into two groups on the basis of median plasma concentration of ANP, Gottlieb et al. (1989) found a significantly higher mortality rate in those patients with a median plasma ANP concentration greater than 125 pg/ml. Davis et al. (1992) extended these findings and identified ANP as a specific and sensitive test for predicting the development of heart failure in elderly subjects. The results from these studies indicate that plasma ANP concentrations could be used to identify asymptomatic patients at risk for CHF, suggesting that ANP could be used for prevention, detection, and efficacy of treatment strategies.

Plasma ANP concentrations are increased in both healthy persons and CHF patients during an acute bout of exercise (Mannix et al., 1990; Saito et al., 1987; Tanaka et al., 1987). Saito et al. (1987) and Tanaka et al. (1987) documented a relationship between exercise intensity and ANP levels, however, their conclusions regarding the onset kinetics of ANP are not consistent. Saito et al. (1987) did not find an increase in plasma ANP during mild exercise (50%HRmax), while exercise performed at 85% of the predicted maximum resulted in a 105% increase in circulating ANP. On the contrary,

Tanaka et al. (1988) noted a significant increase in ANP beginning at 30%VO_{2max} and a nearly sixfold increase at 90%VO_{2max}. Thus, even though the precise kinetics of ANP production during exercise are not firmly established, it appears that exercise intensity is a prime factor to consider when exercise is employed to stimulate ANP production.

Several studies have also demonstrated a significant rise in plasma ANP during dynamic exercise in patients with CHF (Donckier et al., 1991; Keller et al., 1988; Nicholls et al., 1992; Petzl et al., 1987; Raine et al., 1986; Sigurdsson et al., 1994). Keller et al. (1988) and Petzl et al. (1987) reported significant increases in plasma ANP during an acute bout of exercise and contributed this rise to increases in left atrial pressure as well as right atrial distension. Other studies, however, have reported a response comparable to normals (Donckier et al., 1991), or a relatively blunted response, especially in patients with more severe disease (Nicholls et al., 1992; Raine et al., 1986). Although, the blunted response is not clearly understood, it is thought to be the result of cardiac myocyte depletion and/or a mere reflection of the lower exercise intensity (Agnoletti et al., 1990).

Contrary to the expected inverse relationship between ANP and the antinatriuretic / pressor hormones, plasma concentrations of NE, PRA, ANG II, ALDO, AVP, and ANP increase during dynamic exercise. Mannix et al. (1990) conducted a study to determine the association of ANP with the PRA-ANG II-ALDO axis as well as the rate of ANP secretion during incremental exercise. The results indicated that the parallel increases in ANP and the hormones of the RAAS, along with significant positive relationships among these variables, suggest that there is a dissociation between these systems during exercise and that each may be responding to independent stimuli. Thus, high intensity exercise, like

CHF, may induce physiological conditions in which the normal inverse relationship between the ANP and RAAS axis is significantly perturbed (Mannix et al., 1990).

Considering the potential role of ANP in fluid regulation, additional studies are needed to determine the relative concentrations of the biologically active form α-ANP, and the less biologically active *B*-ANP in patients with CHF. Studies are also needed to determine relative secretion rates of each subtype and the interaction between increases in plasma ANP levels and cardiac output during graded exercise. Furthermore, there appears to be a lack of studies in the existing literature quantifying the relationship between exercise-induced plasma volume kinetics and ANP concentrations.

Plasma Volume Shifts and Pharmacokinetics

Several of the pathophysiological adaptations of CHF influence fluid regulation, vascular reactivity and permeability. Integrity of the vascular wall may be compromised due to chronically elevated neurohormone-induced alterations in vasomotor tone, increases in arterial wall sodium and water content, increases in edema-induced vascular compression, and/or structural changes in vascular morphometry (Derman et al., 1995; Drexler et al., 1991a; LeJemtel, 1986; Sinoway et al., 1987; Zelis et al., 1968, 1970, 1991). Fluid retention and associated extravascular edema in both pulmonary and skeletal muscle tissues contribute to the cardinal symptoms of CHF; exercise intolerance, shortness of breath, and chronic fatigue.

Recognizing that vascular permeability may be altered with the pathophysiological processes associated with CHF, normally occurring exercise-induced fluid shift kinetics

may also be compromised. In healthy adults, exercise produces large fluxes of fluid out of the vascular bed into extravascular compartments (Greenleaf et al., 1979b; Kjellmer, 1964; Lundvall et al., 1972; Mohsenin & Gonzalez, 1984; Sjogaard & Saltin, 1982). This exercise-induced fluid shift is primarily dependent upon factors influencing capillary exchange dynamics as described by Starling (1895) and Landis (1927). They include transcapillary hydrostatic and colloid osmotic pressures, plasma and interstitial osmolality, and vascular permeability. Although the relative importance of these factors are controversial, it has been suggested that increased osmolality during exercise (Greenleaf et al., 1979a; Lundvall et al., 1972) and elevation in capillary hydrostatic pressure and increased capillary surface area (Kjellmer, 1964; Sjogaard & Saltin, 1982) are primarily responsible for fluid translocation during exercise. In a reciprocal manner, plasma colloid osmotic pressure and interstitial fluid pressure become increasingly important in opposing intra- to extravascular plasma volume (PV) shifts during maximal exercise (Mohsenin & Gonzalez, 1984). The alterations influencing vascular permeability described above may affect these factors and therefore fluid translocation during exercise in CHF patients.

Several studies have described changes in PV during exercise testing in healthy adults (Convertino et al., 1980, 1981; Galbo et al., 1975; Senay et al., 1980; VanBeaumont et al., 1972; Wilkerson et al., 1977). In a review on fluid shifts during maximal exercise, Senay and Pivarnik (1985) indicated that, dependent upon the subject's training status and exercise modality, PV appears to decrease in a linear fashion inversely related to exercise intensity. The authors reported that PV decreases approximately 2-4% at 40% peak oxygen consumption (VO_{2peak}), 7-10% at 70% VO_{2peak}, and 12-16% at VO_{2peak} in healthy adults (Senay & Pivarnik, 1985). However, several methodological

limitations of these original studies include the use of inappropriate calculations for PV determinations and inconsistent standardization of postural positioning that affects hematologic variables obtained during blood sampling (Costill & Fink, 1974; Hagan et al., 1980: Senay et al., 1980; VanBeaumont et al., 1972; Wilkerson et al., 1977).

Although the PV changes during acute exercise in healthy adults, the question as to whether PV changes also occur in CHF patients remains to be determined. A study conducted by Feigenbaum et al. (In review, 1997) indicated that CHF patients experience similar plasma shift dynamics with maximal exercise. The 10.6% decrease in PV occurring in CHF patients is similar to the PV shift reported in the literature for healthy adults (Senay & Pivarnik, 1985). This indicates that the exercise-induced PV shift appears to be dependent on exercise intensity (VO_{2peak}) and independent of exercise capacity [CHF patients = 13 $ml \cdot kg^{-1} \cdot min^{-1}$; healthy young adults (literature) = 55 $ml \cdot kg^{-1} \cdot min^{-1}$] (Galbo et al., 1975; VanBeaumont et al., 1981; Wilkerson et al., 1977). The small difference between the relative PV shift observed in the study by Feigenbaum et al. (1997) (10.6%) and those reported for healthy adults (12-16%) may be attributed to the fact that CHF patients and/or supervising physicians are more likely to terminate the SL-GXT prematurely due to the onset of symptoms (i.e. angina, dyspnea) which do not normally limit peak exercise performance in healthy adults.

Although the PV shifts are similar at peak exercise for CHF patients and healthy adults, the question remains as to whether the PV shift is a function of exercise intensity in CHF patients. Only a few studies have examined the changes in PV over a range of exercise intensities and the hypothesis that PV changes are an inverse linear function of exercise intensity remains controversial. Several studies indicate that decreases in PV may

be a linear function of exercise intensity (Convertino et al., 1981; Costill & Fink, 1974; Galbo et al., 1975; Miles et al., 1983), whereas others suggest that the linear relationship exists between rest and approximately 65% VO_{2peak} at which point a "break" occurs and PV decreases in a curvilinear manner (Wilkerson et al., 1977). Further research evaluating PV shifts at submaximal and maximal workloads in both healthy and diseased populations is needed to determine whether the PV shift is a linear function of exercise intensity.

The potential for differences in fluid shift kinetics would have important implications in designing pharmacological treatment strategies and exercise rehabilitation programs for CHF patients. In healthy adults, exercise-induced flow-mediated vasodilatation in resistance vessels increases blood flow through capillary channels thereby improving nutrient supply to active muscle and up regulating metabolic function (Mohsenin & Gonzalez, 1984). However, although the aqueous portion of plasma may shift to extravascular spaces, the concentration of hematocrit (Hct), plasma proteins (PP), neurohormones (i.e. PRA, AVP, ANP), and pharmacological agents have been shown to increase substantially during exercise in healthy subjects (Convertino et al., 1980, 1981, 1983; Hartley et al., 1972; Hurwitz et al., 1983; Senay & Pivarnik, 1985; Van Baak et al., 1990, 1992). Although only a limited number of studies have evaluated the effect of exercise on the pharmacokinetics of drugs, it is clear that exercise does influence the pharmacokinetics of certain drugs including propranolol (Henry et al., 1981; Hurwitz et al., 1983; Van Baak et al., 1990, 1992), verapamil (Van Baak et al., 1992), and several other medications commonly prescribed for cardiac patients (Van Baak, 1990). CHF Pharmacotherapy is currently designed to improve the inotropic state of the myocardium (cardiac glycosides), relieve circulatory congestion (diuretics), unload the myocardium

(vasodilators), and reduce the potential risk of blood coagulation in coronary and cerebral arteries and smaller vascular beds (anticoagulants).

Interestingly, both cardiac glycosides (i.e. digitalis) and anticoagulants (i.e. coumadin, warfarin) have narrow dose-response therapeutic limits. Consequently, exercise-induced plasma volume shifts could substantially increase intravascular drug concentrations and potentially increase the risk of pharmacotherapy-induced morbidity (i.e. cardiac arrhythmias, hemorrhaging). Recognizing the increasing acceptance of daily cardiac rehabilitative exercise programs as an effective intervention strategy, exercise-induced increases in plasma drug concentrations as well as endogenous neurohormones could theoretically alter drug efficacy and should be considered when prescribing pharmacotherapy and exercise.

In addition, there are many other issues involving pharmacotherapy-neurohumoral interactions during exercise in CHF patients which should be considered. For instance, potent inotropic agents may reflexly reduce systemic vascular resistance by improving cardiac output, but these effects are largely indirect and are usually not specifically designed to selectively inhibit the neurohumoral axis in CHF during exercise. Further, diuretics and vasodilators, although obviously beneficial, are well known to further activate neurohumoral mechanisms such as ANP which already becomes hypersecreted during exercise (Olivari et al., 1983). Diuretics are commonly prescribed to patients with CHF to enhance diuresis and reduce congestion and/or edema. However, their effectiveness in returning blood volume to pre-disease levels has not been established.

Additional studies designed to determine the temporal pattern of PV shifts during graded exercise are needed to provide a better understanding of fluid kinetics in patients

with CHF. Furthermore, studies evaluating exercise-induced fluid shifts and subsequent hemoconcentration in diseased populations may have important implications in evaluating the efficacy of pharmacological agents. The findings may result in a better understanding of the acute exercise response in CHF patients and subsequent recommendations for exercise programs.

Cardiac Response to an Acute Bout of Exercise

During exercise, cardiac output (CO) increases to match the demand for increased blood flow, oxygen and nutrients to the working muscles. The increase in CO during acute exercise can be accomplished through an increase in heart rate (HR) and/or stroke volume (SV). In general, CHF patients demonstrate characteristic responses to dynamic exercise. However, as functional class declines there is a progressive decrease in peak CO, SV, and HR (Hanson, 1994).

Cardiac output is defined as the quantity of blood pumped by the heart each minute and is the product of the blood volume ejected with each beat [stroke volume (SV)] and HR (Guyton, 1996). Cardiac output and blood flow distribution determines the supply of substrate and oxygen delivered to tissues and, in healthy adults, has been shown to increase four to seven fold during heavy exercise to support the increase in metabolic demand (Guyton, 1996). Consequently, CO is a primary determinant of exercise capacity and tolerance. It is likely that the reduced cardiac output to work relationship in CHF causes hypoperfusion of both working skeletal muscles and visceral organs, which leads to early anaerobic metabolism and fatigue (Sullivan & Cobb, 1992).

Cardiac output is dependent upon the ability of the heart to fill and eject a given quantity of blood within a myocardial cycle. Myocardial filling is dependent on filling pressure (preload), venous return, and systemic blood volume whereas ventricular ejection is dependent on myocardial contractility and vascular resistance (afterload). The relationship between myocardial filling and ejection is best described by the Frank-Starling law of the heart which states that the "energy of contraction, however measured, is a function of the length of the muscle fibers prior to contraction" (Sarnoff, 1954). Increases in venous return and subsequent volume of blood entering the ventricles during diastole leads to an inherent stretch and an increase in end-diastolic dimension (Horwitz et al., 1972). The increased stretch causes the actin and myosin filaments of the cardiac myocytes to reset/overlap at a length closer to the muscles optimal force generating capacity (length-tension relationship). This results in an increase in contractile force during systole and a larger ejection fraction. As expected, there is a strong correlation between end-diastolic dimension, contractility, and SV (Higginbotham et al., 1986).

In healthy adults, CO increases as a function of exercise intensity with SV accounting for a substantial proportion of the increase up to 50% VO_{2peak} (Astrand et al., 1964). At exercise intensities greater than 50% VO_{2peak}, increases in CO are thought to be almost entirely due to increases in HR (Higginbotham et al., 1986; Spina, et al., 1992). The increase in SV up to 50% VO_{2peak} appears to be due to a combination of mechanisms, the first of which is the Frank-Starling mechanism described above. The second mechanism is the sympathetic-mediated catecholamine-induced adrenergic stimulation of the myocardium which improves contractility independent of the Frank-Starling mechanism. During moderate exercise, SV increases with increasing adrenergic

stimulation and end diastolic dimension until either a peak chamber volume is reached or the period of diastole between the contractions becomes so reduced that blood does not have time to flow adequately from the atria into the ventricles (Higginbotham et al., 1986). At the point during exercise when SV plateaus, sympathetic-mediated increases in HR are responsible for further increases in CO.

Maximal HR and subsequently, maximal CO, declines with aging and may be due to decreased end-organ sensitivity to catecholamines (Stamford, 1988). Although it has been observed that the physiological processes associated with aging does not appear to influence beta-adrenergic receptor number or affinity (Guarnieri et al., 1980), the observed decrease in chronotropic and inotropic responsiveness to beta-adrenergic stimulation could be due to changes in aged beta-adrenergic receptors (Dillon et al., 1980; Feldman et al., 1984) or a postsynaptic breakdown in the receptor-effector coupling (Lakatta, 1980). Interestingly, despite the downregulation of sympathetic-mediated responses in the elderly, exercise CO is maintained at submaximal workloads through compensatory mechanisms influencing cardiac dilation and increasing SV. In comparison to the sympathetic-mediated chronotropic and inotropic responses in their younger counterparts, the ability to increase SV at a given relative exercise workload in the elderly results from increases in both time for diastolic filling and reliance on the Frank-Starling mechanism. Although the increased SV offsets the decline in maximal HR, the increased dependence on the Frank-Starling mechanism depends on the absence of underlying disease (i.e. CHF).

If myocardial tissue becomes severely damaged (i.e. myocardial necrosis), the pumping ability of the heart is immediately depressed. As a result, CO is reduced and blood begins to damn in the veins contributing to an increase in venous pressure. In

patients with CHF, failure of the heart to pump blood at a rate equivalent to meet the requirements of the metabolizing tissues results in the rapid activation of the neurohumoral systems (i.e. NE, RAAS, AVP), which in turn, result in hypervolemia, increased vasomotor tone, and increased ventricular filling as described previously. Although myocardial infarction-induced wall motion abnormalities and chamber dilation can reduce left ventricular ejection fraction (LVEF) by 30-40%, the increases in venous return, reliance on the Frank-Starling mechanism, circulating catecholamines, and prescribed pharmacotherapy (i.e. digitalis) compensate and relative SV and subsequently CO are not compromised at rest. Considering that standard pharmacotherapy includes beta-adrenergic blockers and that beta-adrenergic receptors may already be down-regulated (due to chronically heightened sympathetic activity), the increases in SV during exercise induced by circulating catecholamines may be attenuated in patients with CHF. When compared to the healthy age-matched elderly, CHF patients may experience greater concentrations of ANG II and AVP at lower relative workloads and, in conjunction with the expanded PV and the beta-blocker-induced slower HR response, could result in larger increases in end-diastolic volume (preload). Furthermore, the increase in preload, increased reliance on the Frank-Starling mechanism, and possibly the increase in plasma concentrations of prescribed digitalis glycosides resulting from intensity-specific exercise-induced plasma shifts could result in increases in SV accompanying increases in exercise intensity. Consequently, it remains to be determined whether CHF patients on standard pharmacotherapy exhibit intensity-related increases in SV in a similar fashion as healthy elderly subjects during acute exercise.

Summary

In summary, it has been established that the level of neurohumoral activation is highly correlated with morbidity in CHF (Cohn, 1992). However, one problem associated with neurohumoral hyperactivity in patients with CHF is that the normal neurohumoral profile at rest may be relatively normal. Consequently, measurements taken during resting conditions may not be representative of abnormal neurohumoral responses which occur during normal daily activities or during traditional exercise rehabilitation programs (Dzau et al., 1981; Sigurdsson et al., 1994). In contrast, acute exercise may unmask such abnormalities and provide the clinician with an opportunity to determine an more appropriate treatment strategy.

To date, the temporal pattern of many neurohumoral responses (i.e. AVP, α-ANP vs. *B*-ANP) and/or interactions with cardiac hemodynamics occurring during the transition from rest to exercise in CHF are unknown. Furthermore, the effects of exercise-induced PV shifts and subsequent hemoconcentration of neurohormones and prescribed medications remains to be determined. Finally, more research is needed to determine whether standard CHF pharmacotherapy adequately regulates circulating fluid volume. A more thorough understanding of the factors that regulate the neurohumoral axis in CHF patients may eventually allow clinicians to selectively manipulate the release of neurohormones.

CHAPTER 3
METHODOLOGY

Subject Characteristics

Fifteen patients with CHF secondary to CAD (NYHA classification II or III; LVEF $\leq$ 50%) who were on standard CHF pharmacotherapy were recruited from the Department of Medicine, Cardiology Section, University of Florida and the Veterans Administration Medical Center (VAMC) to participate in this prospective, controlled study. Nine healthy age- and weight-matched sedentary individuals, who served as controls, were recruited from the Gainesville community. The study involved four visits to the Center for Exercise Science (CES) (approximately 1.5 hours per visit) over a two week period. Procedures for this study were approved by the University of Florida College of Medicine Institutional Review Board (Appendix A).

Preliminary screening of the CHF patients was performed by clinical personnel from the Shands Hospital Cardiology Section. Criteria for the inclusion of the CHF patients were as follows; (1) age 18 or older with known CHF, (2) left ventricular ejection fraction (LVEF) $\leq$ 50% documented by cardiac catheterization or echocardiography within the previous six months, (3) optimal drug therapy (e.g. digitalis glycosides, ACE-inhibitors, diuretics), (4) etiology of ischemic heart disease, (5) CAD documented by myocardial infarction and/or cardiac catheterization, and (6) New York Heart Association

classification II or III. Criteria for the exclusion of the CHF patients were as follows; (1) acute unstable myocardial ischemia and/or angina, (2) recent myocardial infarction within six weeks, (3) patients with uncontrolled hypertension and/or diabetes or renal failure, (4) patients with chronic lung disease, (5) patients with cardiac pacemakers, and (6) patients with orthopedic problems and/or peripheral vascular disease that would limit exercise.

The control group consisted of nine subjects that were selected to match the CHF patients as closely as possible with respect to gender, age, and body composition. Subjects in the control group were to be normally active but not athletic and have no evidence of cardiovascular disease as determined by clinical examination, medical history, and graded exercise testing. Following the orientation session (Day 1), subjects were required to report to the CES for experimental testing on three days separated by a minimum of 72 hours. The series of tests on the second day were designed to measure body composition, peak systemic oxygen consumption (VO_{2peak}), peak heart rate (HRpeak), neurohormone activity, exercise-induced plasma volume (PV) and blood volume (BV) shifts, and provide exercise intensity criteria to be used during the subsequent day of exercise testing. On the third day, systemic oxygen consumption, neurohormone activity, and PV and BV shifts were to be measured at rest and during treadmill exercise at approximately 40% and 70% HRpeak based on the endpoints from the previous graded exercise test (GXT). On the fourth day, PV was measured using the Evan's Blue Dye dilution technique.

Day 1: Experimental Protocol - Screening and Orientation

Upon arriving at the CES, potential subjects received a comprehensive explanation of the entire research protocol, benefits from participating in the study, inherent risks, and expected commitments with regard to time. Following the explanation of the proposed study, subjects were given time for questioning and further clarification. Subjects who agreed to participate completed a demographic, medical, family, nutritional, smoking, and physical activity history questionnaires (Appendix B). These forms were reviewed by the investigator, and subjects not meeting the requirements of the study were notified and excluded. Documented informed consent was obtained from all subjects who agreed to continue (Appendix C). Subjects were then scheduled for and given instructions for their subsequent visits (Appendix D). All subjects were asked to restrict strenuous physical activity for 24 hours prior to testing sessions and report to the CES laboratory 2-3 hours postprandial. For the purpose of standardization, all subjects were requested to ingest medications approximately two hours prior to testing sessions. During the orientation session, subjects were made familiar with all aspects of the study including the procedures for the treadmill GXT and techniques for blood sampling and analysis.

Day 2: Experimental Protocol

Medical Evaluation

For visit 2, the subjects reported to the CES for approximately 1.5 hours in the morning. During this visit and subsequent visits subjects completed a 24-hour history

questionnaire before testing (Appendix E). The subject was seated in a quiet room for 15 minutes whereafter resting heart rate and blood pressure were obtained using standard auscultation procedures and a Trimline mercury sphygmomanometer (Pymah Co., Somerville, NJ). Body composition was assessed anthropometrically from the sum of 7 skinfold fat sites (chest, axilla, triceps, subscapular, abdominal, suprailium, and thigh). All measurements were obtained from the right side of the body with a Lange skinfold caliper (Cambridge Scientific Industries, Cambridge, MD). The methods for obtaining skinfolds and measures of body composition have been outlined by Pollock & Wilmore (1991).

Following this evaluation a medical examination was performed by qualified personnel and a 20 gauge polyethylene cannula was placed into an antecubital vein of the right arm. The medical examination included a general evaluation and assessment of cardiac function and clinical symptoms. Catheter placement was performed under aseptic conditions and kept open by filling the catheter with dilute heparinized saline.

Graded Exercise Test

Following the baseline evaluation, each subject was prepared to undergo a walking GXT to determine VO_{2peak}. The GXT consisted of using an incremental treadmill (Quinton Instruments, Seattle, WA) protocol (Modified-Naughton) (Naughton, 1973). The initial workload on the treadmill was 2.0 mph for CHF patients (3.0 mph for CON subjects) at 0% grade and progressed every 2 minutes by increasing the grade by 2% until the subject reached voluntary maximal exertion or became symptomatic with positive hemodynamic or medical indices.

The following criteria recommended by the ACSM were used for termination of the GXT (American College of Sports Medicine, 1995):

1. Fatigue,
2. Failure of monitoring equipment,
3. Light-headedness, confusion, ataxia, cyanosis, dyspnea, nausea or any peripheral circulatory insufficiency,

4a. Onset of grade II/III angina pectoris (moderate to severe) with exercise,

b. Mild angina pectoris with 2 mm of ST segment depression,

5. Symptomatic supraventricular tachycardia,
6. "ST" segment displacement 4 mm or greater in the absence of angina pectoris,
7. Ventricular tachycardia [3 or more consecutive premature ventricular contractions (PVC)],
8. Exercise induced left bundle branch block;
9. Onset of second and/or third degree atrial-ventricular block,
10. R on T PVC's (one),
11. Frequent multifocal PVC's (30% of the complexes),
12. Excessive hypotension (greater then 20 mm Hg drop in systolic blood pressure during exercise),
13. Excessive blood pressure rise: systolic blood pressure greater or equal to 220 or diastolic blood pressure greater or equal to 110 mm Hg,
14. Inappropriate bradycardia: drop in heart rate greater than 10 beats.min^{-1} with an increase or no change in workload.

During the test, expired gases were collected through a low-resistance two-way valve (Hans Rudolph Inc., Kansas City, MO). Samples of the expired gases were analyzed using a metabolic cart (CPX Medical Graphics Corporation, St. Paul, MN). The system was calibrated with standard gases of known concentrations before and after each test. Minute ventilation (VE) was determined by an electronic flow meter on the expired side of the circuit. Volume calibration was performed with a 3-liter calibration syringe. Analog outputs from each device was continuously monitored by an on line microcomputer via an analog-to-digital conversion board. This provided breath by breath determination of VO_2, VCO_2 and VE.

Heart rate, and 12 lead electrocardiogram (ECG) were monitored and recorded throughout the test and 10 minutes into recovery using standard lead placement with a Quinton Q 4000 system (Quinton Instruments, Seattle, WA). Blood pressure measurements were obtained every two minutes during the test and 10 minutes into recovery using a standard sphygmomanometer. Ratings of perceived exertion (RPE), and symptoms of angina and/or dyspnea were obtained at the end of each minute throughout the test using the 15 point Borg's perceived exertion scale (Borg, 1982), and the 4-point dyspnea and angina scales recommended by the ACSM, respectively (American College of Sports Medicine, 1995).

Two minutes prior to the start of exercise a 30 ml blood sample was obtained. The blood sample was drawn into two plastic syringes and separated in individual aliquots for norepinephrine (NE), angiotensin II (ANG II), arginine vasopressin (AVP), aldosterone (ALDO), α-atrial natriuretic peptide (α-ANP), *B*-atrial natriuretic peptide (*B*-

ANP), hemoglobin (Hb), and prescribed pharmacotherapy (i.e. digitalis) assays (see section entitled "Blood Sample Analyses"). To determine the response to acute exercise and timecourse of recovery, additional 30 ml blood samples were obtained immediately post-exercise and at 10 and 20 minutes of recovery. For the purpose of standardization all blood samples were obtained in the upright position.

Following the final blood draw patients were allowed to recover 20 minutes in a quiet room. Prior to discharge vital signs were once more obtained and if the patient was deemed suitable to continue in the study a follow-up visit was scheduled.

Day 3: Experimental Protocol - Submaximal Exercise Tests

Subjects reported to the CES for the second series of experiments a minimum of 72 hours but not more than one week after the second visit. In order to control for a possible effect of circadian rhythms and/or environmental conditions the exercise tests on Day 3 were performed at approximately the same time of day (9:00am-12:00pm) as the GXT on Day 2 To determine the temporal pattern of cardiopulmonary, hemodynamic, and neurohormonal responses during exercise, each subject was studied at two submaximal levels of exercise intensity.

Cardiopulmonary, hemodynamic, and neurohumoral measurements were obtained prior to treadmill exercise and at two submaximal workloads (40% and 70% of HRpeak based on HRpeak determined during the GXT at Visit 2). During each submaximal workload, a three to five minute ramping protocol was to be used to progressively increase the subject's HR to the pre-designated level [(1) workload #1; 40% HRpeak, (2)

workload #2; 70% HRpeak]. Measurements were obtained after the designated HR was maintained for a 3 to 5 minute steady-state period. Each of the two submaximal workloads were to last 10 minutes and separated by a 20 minute rest period.

Similar procedures as previously described were used to obtain blood samples (30 ml) for the determination of hemoglobin and plasma concentration of neurohormones and prescribed medications. Blood samples were collected prior to the exercise session and immediately following the steady-state period at each submaximal workload.

Throughout the test, simultaneous recordings for heart rate, and 12 lead ECG's were obtained at 1 min increments using a standard 12 lead placement and a Quinton Q-4000 system (Quinton Instruments, Seattle, WA). Blood pressure measurements, RPE's, and clinical symptoms were also obtained at the end of each minute throughout the test using a standard sphygmomanometer, Borg's RPE scale (Borg, 1982), and the scales recommended by ACSM (American College of Sports Medicine, 1995), respectively. The same criteria for termination of the GXT during visit 2 were used during the third visit.

Day 4: Experimental Protocol - Plasma Volume Measurement

Subjects reported to the CES for the third series of experiments a minimum of 72 hours after the third visit. To determine the effect of ACE-inhibitor and diuretic pharmacotherapy on fluid volume expansion in patients with CHF, PV was measured by indicator dilution technique using Evan's Blue Dye (T-1824). With the subject supine, a 22 gauge polyethylene catheter attached to a saline lock for blood sampling was inserted into a small vein on the subject's right forearm. A butterfly infusion catheter was inserted

into a forearm or wrist vein on the left arm. Twenty minutes post-insertion, a 5 ml venous sample was drawn into a heparinized vacutainer to provide plasma that was used in the generation of the Blue Dye standard. A known quantity (2.5 ml) of a 0.5% aqueous T-1824 solution was injected over a two minute interval into the butterfly catheter and a 6 ml blood sample was drawn into a heparinized vacutainer at 10 minutes post-infusion via the sampling catheter. The syringe and butterfly catheter were weighed prior to and immediately post-infusion of the Blue Dye to determine the precise amount administered. Collected blood samples were transferred to sodium heparinized vacutainers (Vacutainer, Becton-Dickinson, Rutherford, NJ). Whole blood hematocrit and hemoglobin were measured (see section entitled "Blood Sample Analyses"). The remaining blood was centrifuged (Sorvall RT6000B) at 3000 rpm for 10 minutes. Separated plasma was stored in polypropylene tubes at -70°C.

Plasma Volume Analysis

Plasma volume analysis using Evan's Blue Dye (T-1824) is based on the methods of Young et al. (1973) and Greenleaf et al. (1979a). The dye from the plasma sample was extracted onto a wood-cellulose powder (Solka Floc SW 40A) chromatographic column after it had been separated from the albumin by the action of a detergent (Teepol 610 in 2% Na_2HPO_4). Interfering substances such as pigments, proteins, and chylomicrons were washed from the column with 2% Na_2HPO_4. The dye was eluted from the column with a 1:1 acetone-water mixture. The addition of KH_2PO_4 buffered the pH of the eluate to 7.0; absorbance of the eluate was read at 615 nm on a spectrophotometer (Spectronic 710,

Bausch and Lomb). Plasma volume was determined from plasma concentrations of T-1824 using standard indicator dilution formulas:

$$PV = \frac{(V \times D)(St \times v)}{1.03\ (T)}$$

where	V	=	volume (ml) of T-1824 dye injected (22.6 mg/5ml)
	D	=	dilution of standard (1:250)
	St	=	absorbance of the standard
	v	=	volume of the sample extracted (1.0ml)
	T	=	absorbance of the plasma sample
	1.03	=	correction factor for dye uptake by tissues

Blood volume (BV) was calculated as (PV)(100)/[100 - (0.91xHct)].

Red cell volume (CV) was calculated as BV(Hct)/100.

Blood Sample Analyses

Blood was obtained from an indwelling plastic catheter immediately pre- and post-exercise and at 10 and 20 minutes of recovery after the GXT on the first day of testing; immediately pre- and post-exercise for each of the two 10 minute submaximal workload on the second day of testing; as well as prior to and 10 minutes post-Evan's Blue dye injection on the final day of testing. For the purpose of standardization, blood samples collected during the exercise sessions was obtained with the subject standing. A total of 120 ml of venous blood was obtained during the GXT session, 90 ml during the submaximal exercise session, and 12 ml during the PV measurement session. Blood samples were drawn after aspirating and discarding the contents of the catheter and tubing deadspace (~1 ml).

Immediately before and after each testing session a small blood sample (2 ml) was separated and measured for Hb and Hct as described in the following section. Blood samples that were to be assayed for prescribed medications (i.e. digitalis) (10 ml) were added to a chilled vacutainer containing ethylene diamine-tetraacetic acid (EDTA).

Blood samples for neurohormone analyses were withdrawn into a plastic syringe containing no additives and immediately separated into individual aliquots. Blood for NE assay (2 ml) was added to a chilled heparinized vacutainer containing 40 microliters of antioxidant consisting of ethylene glycol-tetraacetic acid (EGTA, 90 mg/ml) and reduced glutathione (75 mg/ml) (Sigma Chemical, St. Louis, MO). Blood for ANG II, ALDO, AVP, α-ANP, and *B*-ANP, assays (10 ml) were added to a chilled vacutainer containing EDTA. Blood samples were immediately mixed and plasma or serum was separated by centrifugation (Sorvall RT6000B) at 3000 RPM at 4°C for 20 minutes. The plasma was pipetted to polypropylene tubes and frozen (Forma Scientific Freezer) at -70°C until the end of the study so that all samples for each subject could be analyzed in the same assay.

Hemoglobin and Hematocrit

Hemoglobin (Hb) was measured in triplicate using the cyanmethemoglobin method (Sigma Diagnostics, St. Louis, MO). Hematocrit (Hct) was measured in triplicate with a microhematocrit centrifuge (IEC, Model MB, Needham Heights, MA) and a Fisher Microcapillary Tube Reader. Hematocrit was corrected (x0.91) for trapped plasma and for whole body Hct.

Calculation of Blood Volume, Red Cell Volume, and Plasma Volume

The relative changes in blood volume (BV), red cell volume (CV), and PV were calculated according to the equations by Dill & Costill (1974). The BV at peak exercise was calculated based on pre- to peak-exercise-induced changes in Hb with the pre-exercise BV based on a relative volume of 100 ml [$BV_{peak} = BV_{pre}$ (Hb_{pre} / Hb_{peak})]. Change in BV was calculated as: $BV(\%) = 100 (BV_{peak} - BV_{pre}) / BV_{pre}$. Hematocrit determined prior to exercise was defined as CV_{pre}. Cell volume $_{peak}$ was calculated from BV_{peak} and Hct_{peak} ($CV_{peak} = BV_{peak} \times Hct_{peak}$). The change in CV was calculated as: $CV(\%) = 100 (CV_{peak} - CV_{pre}) / CV_{pre}$. The PV_{pre} and PV_{peak} were calculated by subtracting the CV from the BV as determined above. The change in PV with exercise was subsequently calculated using: $PV(\%) = 100 (PV_{peak} - PV_{pre}) / PV_{pre}$.

Angiotensin II Radioimmunoassay

Plasma angiotensin II concentration was measured by radioimmunoassay (RIA) in the laboratory of Dr. R. Braith (Department of Exercise and Sport Sciences, University of Florida) and Dr. C. Wood (Department of Physiology, University of Florida). Antibody raised in rabbits against ANG II conjugated to bovine thyroglobulin via glutaraldehyde was used for RIA. The cross-reactivity with ANG III was <27%. Cross-reactivity with ANG I, renin substrate tetradecapeptide, (Sar^1, Ala^8)-ANG II, (Sar^1, Ile^8)-ANG II, ACTH, and AVP were all <0.1%. ANG II was extracted from plasma by absorption onto bentonite and reconstituted in 0.05 M Tris buffer (0.3% bovine serum albumin, 0.01% sodium azide; pH 7.4). ^{125}I-ANG II was used as the tracer. The range of the standard

curve was from 0.38 to 25 pg/tube with a 50% displacement of ^{125}I-ANG II with 2.4 pg/tube. The intra-assay coefficient of variation for a pool of 7.0 pg/tube was 10.5% and the interassay coefficient of variation for the same pool was 10.3%. This assay has been described in previously (Braith et al., 1992).

Aldosterone Radioimmunoassay

Plasma aldosterone concentration was measured using the RIA technique in unextracted serum using a kit available through Diagnostics Products Corp. (Los Angeles, CA). Plasma samples (0.200 ml) were added to polypropylene tubes coated with antibodies to ALDO. Approximately 1 ml of ^{125}I-ALDO tracer was added to the tubes and after 3 hour incubation at 37°C the supernatant was decanted and the tubes counted on a gamma counter. Aldosterone concentration was determined from a standard curve. Intraassay coefficient of variation for this procedure in human samples is 2.7-8.3% and interassay coefficient of variation is 3.6-10.4%. The detection limit is approximately 16 $pg \cdot ml^{-1}$. This assay has been described in previously (Braith et al., 1992).

Arginine Vasopressin Radioimmunoassay

Plasma arginine vasopressin was measured by RIA using a rabbit anti-AVP antibody. The anti-AVP serum was generated in the laboratory of Dr. R. Braith (Department of Exercise and Sport Sciences, University of Florida) and Dr. C. Wood (Department of Physiology, University of Florida). The anti-AVP serum was generated using AVP covalently linked to bovine thyroglobulin with carbodiimide. The crossreactivity of the antiserum with lysine vasopressin was 0.7%. Crossreactivity with

oxytocin, vasotocin, AVP (fragment 4-9), CRF, ACTH, ANG I, and ANG II was each <0.001%. Arginine vasopressin was extracted from plasma by adsorption to bentonite. Plasma (1.0 ml) was extracted and then reconstituted to 0.25 ml with assay buffer (0.05 M phosphate buffer, pH=7.4 containing 0.01 M EDTA and 0.2% BSA). ^{125}I-AVP was used as tracer. Synthetic hAVP used as a standard was purchased from Peninsula Labs (Belmont, CA). The range of the standard curve was from 0.05 to 10.0 pg/tube. In previous studies, the intraassay coefficient of variation for a low pool (0.40 pg/tube) was 4% and for a high pool was 14%. Interassay coefficient of variation was 7%.

Atrial Natriuretic Peptide Radioimmunoassays

Atrial natriuretic peptides (α-ANP and *B*-ANP) were extracted from thawed plasma samples using a technique described previously by Braith et al. (1996). Plasma (1 ml) was deproteinized by adding 750 *u*l 0.1 mol/liter acetic acid and 1.25 ml methanol. Samples were placed on a rocking shaker for 10 minutes followed by centrifugation at 6,000 rpm for 20 minutes at 4°C. The supernatant was dried by vacuum centrifugation. Radioimmunoassays were performed from kits from Peninsula Laboratories (Belmont, CA) using α-ANP and *B*-ANP antiserum that have a 0% cross-reactivity with human brain natriuretic peptide and C-type natriuretic peptide.

Digoxin Fluorometric Immunoassay

Serum digoxin concentrations were measured at the Greenville Memorial Hospital Clinical Laboratory using the Digoxin Fluorometric Enzyme Immunoassay technique and

the Stratus Digoxin kit / Stratus II Immunoassay System available through American Dade International Corp. Duplicate serum samples (0.2 ml) were added to digoxin antibody coated tabs. Digoxin concentration was determined from a standard curve on a microprocessor within the analyzer. The detection range for this technique is 0.4 - 4.0 ng/ml and the critical value is serum [digoxin] greater than 2.1 ng/ml. Intraassay coefficient of variation (CV) for this procedure in human samples is 5-15%.

Statistical Analyses

All data were summarized as mean $\pm$ standard deviation. The Statistical Analyses System (SAS, 1985) and SPSS for Windows (SPSS, 1993) were used for the management and analyses of data. An alpha level of $p \leq 0.05$ was required for statistical significance. Descriptive data were analyzed using one-way Analyses of Variance (ANOVA) to compare heart failure patients and control subjects. Within subject stability of cardiopulmonary, hemodynamic, and neurohormone variables (pre-exercise) measured during the maximal and submaximal exercise sessions were assessed by a one-way ANOVA. Cardiopulmonary, hemodynamic, and neurohormone data were analyzed for within and between group comparisons using an repeated measures ANOVA. If a significant difference was detected, mean values were compared with a Newman-Keuls post-hoc test.

CHAPTER 4
RESULTS

Subject Characteristics

The baseline characteristics of the 15 heart failure patients who participated in the study to evaluate the acute responses to exercise are presented in Table 4.1. The mean age, height, and weight for the heart failure group (CHF) was 62.7±8.0 yrs, 175.0±6.6 cm, and 92.1±20.1 kg, respectively. The average percent body fat was 26.2±6.6%, with an estimated fat weight of 24.9±10.3 kg and lean body mass of 67.3±7.0 kg. The average duration of heart failure was 5±3 yrs, and the mean LVEF was 31.2±9.7%. The etiology of heart failure was ischemic heart disease in all patients and the average NYHA classification value was 2.5±0.5.

To compare the acute exercise responses, a healthy age- and weight-matched control (CON) group was selected to match the CHF group as closely as possible. The CON subjects were sedentary individuals who had no evidence of underlying disease as determined by previous clinical examination. The mean age, height, and weight for the CON subjects was 67.3±8.2 yrs, 178.9±10.1 cm, and 87.7±15.3 kg, respectively. The average percent body fat was 26.7±5.2%, with an estimated fat weight of 23.9±8.1 kg. The two groups did not differ ($p \geq 0.05$; CHF vs. CON) with respect to age or anthropometric measurements.

Table 4.1. Subject Characteristics		
Variables	CHF Patients (n=15)	Control Subjects (n=9)
Age (yrs)	62.7 ± 8.0	67.3 ± 8.2
Height (cm)	175.0 ± 6.6	178.9 ± 10.1
Weight (kg)	92.1 ± 20.1	87.7 ± 15.3
Fat%	26.2 ± 6.6	26.7 ± 5.2
Fat Weight (kg)	24.9 ± 10.3	23.9 ± 8.1
Duration of CHF (yrs)	5 ± 3	N/A
Heart Failure Etiology	Ischemic Heart Disease	N/A
LVEF(%)	31.2 ± 9.7	N/A
NYHA	2.5 ± 0.5	N/A
Post MI	n = 15	N/A
Post CABG	n = 11	N/A
Hypertension	n = 6	N/A
Diabetes Mellitus	n = 3	N/A
Pharmacotherapy:		
Digitalis Glycosides	n = 10	N/A
ACE-Inhibitors	n = 12	
Diuretics	n = 13	
Anticoagulants	n = 12	
Antihypertensives	n = 9	
Beta-Blockers	n = 8	

Values are mean ± S.D.; CHF=chronic heart failure;
LVEF=left ventricular ejection fraction; NYHA=New York Heart Association;
MI=myocardial infarction; CABG=coronary artery bypass graft;
ACE=angiotensin converting enzyme

The Acute Exercise Response in Heart Failure

Evaluation of Exercise Capacity

The mean values for the cardiopulmonary variables obtained during the SL-GXT and submaximal exercise workloads [(1) 40%$\dot{H}$Rpeak; (2) 70%HRpeak] are summarized in Table 4.2. The average pre-exercise (PRE-EX) VO_2 ($VO_{2pre\text{-}ex}$) increased 196% at 40%HRpeak ($p \leq 0.05$ vs. PRE-EX), 303% at 70%HRpeak ($p \leq 0.05$ vs. PRE-EX), and 368% at peak exercise in the CHF group ($p \leq 0.05$ vs. PRE-EX). In the CON group, $VO_{2pre\text{-}ex}$ increased 406% at 40%HRpeak ($p \leq 0.05$ vs. PRE-EX), 590% at 70%HRpeak ($p \leq 0.05$ vs. PRE-EX), and 770% at peak exercise ($p \leq 0.05$ vs. PRE-EX). The nearly 5-fold increase at VO_{2peak} in the CHF group is approximately 60% of the VO_{2peak} observed in the CON, indicating marked exercise intolerance ($p \leq 0.05$; CHF vs. CON). Comparative changes in VO_2 for CHF and CON are presented in Figure 4.1.

The mean PRE-EX minute ventilation (VE) in CHF was 13.4±4.5 $l.min^{-1}$ and increased 309% at peak exercise ($p \leq 0.05$ vs. PRE-EX) compared to a 650% VE increase in CON ($p \leq 0.05$ vs. PRE-EX). Although the two groups did not differ ($p \geq 0.05$) at the lower intensity workloads, VE for VO_2 (VE/VO_2) at peak exercise (VE/VO_{2peak}) was 3.8 $l/ml.kg^{-1}.min^{-1}$ for CHF compared to 3.3 $l/ml.kg^{-1}.min^{-1}$ for CON. The higher VE/VO_{2peak} in CHF indicated a greater need for VE for a given O_2 uptake.

Cardiocirculatory Responses to Acute Exercise

The mean values for the cardiocirculatory variables obtained during the SL-GXT and submaximal workloads are summarized in Table 4.2. The average PRE-EX heart rate

Table 4.2. Cardiopulmonary Responses During and Following Graded Exercise in Chronic Heart Failure Patients (n=15) and Controls (n=9)

Variables	GRP	PRE-EX	40%HRPK	70%HRPK	PK-EX
VO_2	CHF	287.8 ± 93.8	859.6 ± 280.5*‡	1183.2 ± 443.9*‡	1367.2 ± 481.7*‡
$ml.min^{-1}$	CON	262.7 ± 64.8	1320.6 ± 361.8*	1800.4 ± 464.5*	2262.3 ± 583.7*
VO_2	CHF	3.2 ± 0.8	9.5 ± 2.0*‡	12.9 ± 3.2*‡	15.0 ± 3.6*‡
$ml.kg^{-1}.min^{-1}$	CON	3.0 ± 0.7	15.2 ± 3.7*	20.7 ± 4.4*	26.0 ± 5.8*
VE	CHF	13.4 ± 4.5	26.7 ± 4.9*‡	40.9 ± 10.6*‡	54.9 ± 15.1*‡
$l.min^{-1}$	CON	11.7 ± 1.6	41.0 ± 7.8*	60.1 ± 10.8*	87.7 ± 19.8*
VE / VO_2	CHF	4.3 ± 1.0	2.9 ± 0.9*	3.3 ± 1.1*	3.8 ± 1.1*
$l/ml.kg^{-1}.min^{-1}$	CON	4.1 ± 1.4	2.8 ± 0.5*	2.9 ± 0.4*	3.3 ± 0.5*
HR	CHF	77.3 ± 11.1	95.3 ± 13.4*‡	111.2 ± 18.1*‡	125.1 ± 21.9*‡
$beats.min^{-1}$	CON	75.9 ± 8.5	104.3 ± 11.2*	126.1 ± 16.4*	147.7 ± 22.2*
$HR_{reserve}$	CHF	47.8 ± 16.3‡			
beats	CON	71.8 ± 21.5			
SBP	CHF	121.6 ± 14.6	139.4 ± 19.0*‡	157.6 ± 23.7*‡	172.7 ± 29.3*‡
mm Hg	CON	131.3 ± 12.7	166.7 ± 17.6*	187.3 ± 20.6*	202.0 ± 23.5*
DBP	CHF	77.8 ± 10.9‡	79.6 ± 9.9	83.5 ± 10.6*	87.3 ± 14.0*
mm Hg	CON	87.1 ± 5.8	87.1 ± 8.1	91.8 ± 8.9*	91.3 ± 10.7*
MAP	CHF	92.2 ± 11.3‡	99.4 ± 11.3‡	107.9 ± 13.8*‡	115.5 ± 17.8*‡
mm Hg	CON	101.3 ± 7.5	113.4 ± 10.8*	123.3 ± 10.5*	131.3 ± 13.8*
RPP	CHF	94.1 ± 18.0	134.2 ± 30.5*‡	176.6 ± 46.0*‡	219.6 ± 68.3*‡
(HR x SBP) / 100	CON	99.5 ± 13.4	174.6 ± 31.6*	237.1 ± 47.1*	307.4 ± 51.5*
O_2 Pulse	CHF	3.8 ± 1.6	9.1 ± 3.6*‡	10.9 ± 4.7*‡	11.1 ± 4.2*‡
$ml.beat^{-1}$	CON	3.5 ± 0.9	12.7 ± 3.1*	14.2 ± 2.8*	15.2 ± 2.7*

Values are mean ± S.D.; *$p \leq 0.05$ vs. Pre-Exercise; ‡ $p \leq 0.05$ vs. CON;
GRP=Group; CHF=chronic heart failure patients; CON=control subjects;
PRE-EX=pre-exercise; 40%HRPK=40%HRpeak; 70%HRPK=70%HRpeak;
VO_2=oxygen consumption per minute; VE=minute ventilation; HR=heart rate;
SBP=systolic blood pressure; DBP=diastolic blood pressure; MAP=mean arterial pressure;
RPP=rate pressure product

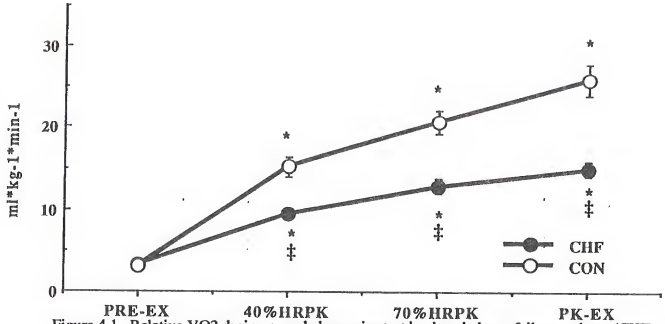

Figure 4.1. Relative VO2 during a graded exercise test in chronic heart failure patients (CHF) and control subjects (CON). PRE-EX=prior to exercise; HRPK= heart rate peak; PK-EX= peak exercise.
* $p<0.05$ vs pre-exercise; ‡ $p<0.05$ vs CON.

(HR_{pre-ex}) increased 23% at 40%HRpeak ($p \leq 0.05$ vs. PRE-EX), 44% at 70%HRpeak ($p \leq 0.05$ vs. PRE-EX), and 62% at peak exercise in the CHF group ($p \leq 0.05$ vs. PRE-EX). In the control group, HR_{pre-ex} increased 37% at 40%HRpeak ($p \leq 0.05$ vs. PRE-EX), 66% at 70%HRpeak ($p \leq 0.05$ vs. PRE-EX), and 95% at peak exercise ($p \leq 0.05$ vs. PRE-EX). Comparative changes in HR for CHF and CON are presented in Figure 4.2.

The mean chronotropic reserve was 47.8±16.3 beats for CHF compared to 71.8±21.5 beats for CON ($p \leq 0.05$; CHF vs. CON). The rate pressure product (RPP) ([beats.min^{-1} * systolic blood pressure]/100), an indicator of myocardial O_2 demand, was estimated at 219.6±68.3 versus 307.4±51.5 at peak exercise, for CHF and CON, respectively ($p \leq 0.05$; CHF vs. CON). The pre-exercise O_2pulse increased 139% at 40%HRpeak ($p \leq 0.05$ vs. PRE-EX), 187% at 70%HRpeak ($p \leq 0.05$ vs. PRE-EX), and 192% at peak exercise in CHF ($p \leq 0.05$ vs. PRE-EX). In CON, O_2pulse increased 263% at 40%HRpeak ($p \leq 0.05$ vs. PRE-EX), 306% at 70%HRpeak ($p \leq 0.05$ vs. PRE-EX), and 334% at peak exercise ($p \leq 0.05$ vs. PRE-EX). Mean values for CON indicated a greater reserve capacity as evidenced by a 24 beat chronotropic reserve difference, a 142% difference in O_2pulse and a 76% larger RPP at peak exercise ($p \leq 0.05$; CHF vs. CON).

The mean PRE-EX systolic blood pressure (SBP_{pre-ex}) increased 15% at 40%HRpeak ($p \leq 0.05$ vs. PRE-EX), 30% 70%HRpeak ($p \leq 0.05$ vs. PRE-EX), and 42% at peak exercise in CHF ($p \leq 0.05$ vs. PRE_EX). In CON, SBP increased 27% at 40%HRpeak ($p \leq 0.05$ vs. PRE-EX), 43% at 70%HRpeak ($p \leq 0.05$ vs. PRE-EX), and 54% at peak exercise ($p \leq 0.05$ vs. PRE-EX). The mean PRE-EX diastolic blood pressure (DBP_{pre-ex}) increased 2% at 40%HRpeak, 7% at 70%HRpeak ($p \leq 0.05$ vs. PRE-EX), and

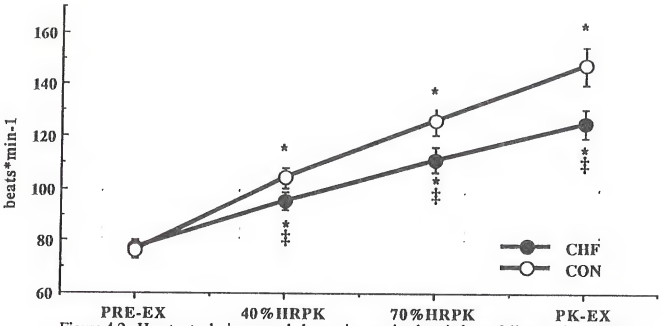

Figure 4.2. Heart rate during a graded exercise test in chronic heart failure patients (CHF) and control subjects (CON). PRE-EX= prior to exercise; HRPK= heart rate peak; PK-EX= peak exercise.
* $p<0.05$ vs pre-exercise; ‡ $p<0.05$ vs CON.

12% at peak exercise in CHF ($p \leq 0.05$ vs. PRE-EX). In CON, DBP did not increase substantially at 40%HRpeak (87.1±5.8 mmHg to 87.1±8.1 mmHg), but did increase 5% at 70%HRpeak and at peak exercise ($p \leq 0.05$ vs. PRE-EX). In addition, the PRE-EX mean arterial pressure ($MAP_{pre\text{-}ex}$) increased 8% at 40%HRpeak, 17% at 70%HRpeak ($p \leq 0.05$ vs. PRE-EX), and 25% at peak exercise in CHF ($p \leq 0.05$ vs. PRE-EX). In CON, MAP increased 12% at 40%HRpeak ($p \leq 0.05$ vs. PRE-EX), 22% at 70%HRpeak ($p \leq 0.05$ vs. PRE-EX), and 30% at peak exercise ($p \leq 0.05$ vs. PRE-EX). Comparative changes in MAP for CHF and CON are presented in Figure 4.3. MAP was significantly greater pre-exercise and at all exercise intensities in CON ($p \leq 0.05$; CHF vs. CON), indicating a desensitization in the neurohumoral-circulatory control system and/or the compensation due to pharmacotherapy (i.e. ACE-Inhibitors, *B*-Blockers) in the CHF patients.

Exercise Tolerance and Time

Ratings of perceived exertion (RPE), clinical symptoms, and peak exercise time achieved during the SL-GXT and submaximal workloads are summarized in Table 4.3. The mean values for RPE, angina, and dyspnea at peak exercise in CHF were 14.8±3.3, 0.4±0.8, and 3.2±0.7, respectively. The mean exercise time on the modified Naughton exercise protocol was 11:36±4:54 min, achieved at a work load of 2 mph and 8% grade. In contrast, the mean values for RPE, angina, and dyspnea at peak exercise in CON were 17.5±2.7, 0, and 1.1±1.5, respectively. The mean exercise time was 16:24±4:00 min and significantly greater compared to CHF ($p \leq 0.05$; CHF vs. CON).

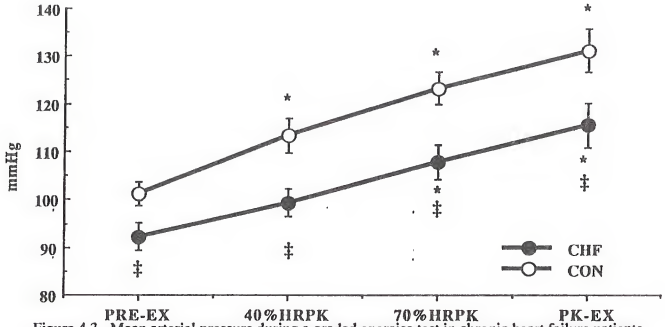

Figure 4.3. Mean arterial pressure during a graded exercise test in chronic heart failure patients (CHF) and control subjects (CON). PRE-EX= prior to exercise; HRPK= heart rate peak; PK-EX= peak exercise.
* $p<0.05$ vs pre-exercise; ‡ $p<0.05$ vs CON.

Table 4.3. Exercise Tolerance and Exercise Time During Symptom-Limited Graded Exercise in Chronic Heart Failure Patients (n=15) and Controls (n=9)

Variables	GRP	PRE-EX	40%HRPK	70%HRPK	PK-EX
RPE	CHF	6.0 ± 0.0	8.7 ± 2.7*	11.4 ± 3.2*	14.8 ± 3.3*‡
(6-20 scale)	CON	6.0 ± 0.0	10.7 ± 2.3*	13.7 ± 2.8*	17.5 ± 2.7*
Angina	CHF	0.0 ± 0.0	0.0 ± 0.0	0.1 ± 0.3	0.4 ± 0.8
(0-4 scale)	CON	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
Dyspnea	CHF	0.1 ± 0.3	0.6 ± 0.9*	1.8 ± 1.2*‡	3.2 ± 0.7*‡
(0-4 scale)	CON	0.0 ± 0.0	0.2 ± 0.7	0.3 ± 1.0	1.1 ± 1.5*
Exercise	CHF				11:36 ± 4:54‡
Time (min)	CON				16:24 ± 4:00

Values are mean ± S.D.; *$p \leq 0.05$ vs. Pre-Exercise; ‡$p \leq 0.05$ vs. CON;
GRP=Group; CHF=chronic heart failure patients; CON=control subjects;
PRE-EX=pre-exercise; 40%HRPK=40%HRpeak; 70%HRPK=70%HRpeak;
PK-EX=peak-exercise; RPE=rating of perceived exertion

Hemodynamic Responses to Acute Exercise

Exercise was associated with a significant change in hemoconcentration, as presented in Table 4.4. In both CHF and CON, hematocrit (Hct) and hemoglobin (Hb) increased with corresponding decreases in PV and BV. The average Hct (corrected) and Hb were 37.7±4.1% and 16.0±1.9 $g \cdot dl^{-1}$ PRE-EX, increasing to 39.2±4.1% and 16.7±1.8 $g \cdot dl^{-1}$ at 40%HRpeak, 39.5±4.3% and 17.4±2.0 $g \cdot dl^{-1}$ ($p \leq 0.05$ vs. PRE-EX) at 70%HRpeak, and 40.4±4.0% ($p \leq 0.05$ vs. PRE-EX) and 18.4±2.2 $g \cdot dl^{-1}$ ($p \leq 0.05$ vs. PRE-EX) at peak-exercise in CHF, respectively. These values indicate a 1.2±1.1% PV decrease and 2.8±1.4% BV decrease at 40%HRpeak, a 5.2±2.1% PV decrease ($p \leq 0.05$ vs. PRE-EX) and 7.7±3.0% BV decrease ($p \leq 0.05$ vs. PRE-EX) at 70%HRpeak, and a 7.9±2.7% PV decrease ($p \leq 0.05$ vs. PRE-EX) and 13.3±2.7% BV decrease ($p \leq 0.05$ vs. PRE-EX) at peak-exercise.

In the control group, Hct and Hb were 40.8±2.3% and 17.5±1.3 $g \cdot dl^{-1}$ PRE-EX, increasing to 41.7±2.2% and 18.6±1.4 $g \cdot dl^{-1}$ at 40%HRpeak, 42.8±2.3% ($p \leq 0.05$ vs. PRE-EX) and 19.5±1.6 $g \cdot dl^{-1}$ ($p \leq 0.05$ vs. PRE-EX) at 70%HRpeak, and 43.5±2.6% ($p \leq 0.05$ vs. PRE-EX) and 20.2±2.7 $g \cdot dl^{-1}$ ($p \leq 0.05$ vs. PRE-EX) at peak-exercise, respectively. These values indicate a 2.7±1.1% PV decrease and 4.1±2.0% BV decrease ($p \leq 0.05$ vs. PRE-EX) at 40%HRpeak, a 4.1±3.0% PV decrease ($p \leq 0.05$ vs. PRE-EX) and 8.7±2.7% BV decrease ($p \leq 0.05$ vs. PRE-EX) at 70%HRpeak ($p \leq 0.05$), and a 7.4±3.1% PV decrease ($p \leq 0.05$ vs. PRE-EX) and 13.1±3.0% BV decrease ($p \leq 0.05$ vs. PRE-EX) at peak-exercise.

Table 4.4. Relative Changes in Blood Volume, Cell Volume, and Plasma Volume During and Following Graded Exercise in Chronic Heart Failure Patients (n=15) and Controls (n=9)

Variable	GRP	PRE-EX	40%HRPK	70%HRPK	PK-EX	REC-10	REC-20
Hct (%)	CHF	41.5 ± 4.5‡	43.1 ± 4.6	43.4 ± 4.8‡	44.4 ± 4.4*‡	43.9 ± 3.9‡	42.9 ± 4.2
	CON	45.1 ± 2.9	45.9 ± 2.5	47.1 ± 2.5	47.7 ± 2.9*	47.1 ± 3.1	46.1 ± 3.0
Hct x.91 (%)	CHF	37.7 ± 4.1‡	39.2 ± 4.1	39.5 ± 4.3‡	40.4 ± 4.0*‡	39.8 ± 3.6‡	39.0 ± 3.8
	CON	40.8 ± 2.3	41.7 ± 2.2	42.8 ± 2.3	43.5 ± 2.6*	42.8 ± 2.8	41.9 ± 2.8
Hb ($g.dl^{-1}$)	CHF	16.0 ± 1.9‡	16.7 ± 1.8‡	17.4 ± 2.0*‡	18.4 ± 2.2*‡	17.7 ± 1.8*‡	17.5 ± 1.9*
	CON	17.5 ± 1.3	18.6 ± 1.4	19.5 ± 1.6*	20.2 ± 1.7*	19.2 ± 1.3*	18.2 ± 1.1
MCHC	CHF	42.4 ± 3.8	42.7 ± 4.1	44.2 ± 3.8*	45.6 ± 3.8*	44.3 ± 3.9*	44.8 ± 3.9*
	CON	42.9 ± 3.9	44.5 ± 3.9	45.6 ± 3.0*	46.4 ± 3.8*	44.9 ± 4.1*	43.4 ± 3.7
CV (ml)	CHF	37.7 ± 4.1	38.1 ± 3.9	36.4 ± 3.9*	36.5 ± 3.7*	36.6 ± 3.3*	36.5 ± 3.5*
	CON	40.8 ± 2.3	39.9 ± 2.1	39.1 ± 2.1	37.8 ± 2.3*	38.8 ± 2.5*	40.1 ± 2.7
BV (ml)	CHF	100.0	97.2 ± 1.4	92.2 ± 3.0	86.7 ± 2.7	92.0 ± 4.7	93.6 ± 4.3
	CON	100.0	95.9 ± 2.0	91.3 ± 2.7	86.9 ± 3.0	90.6 ± 4.9	95.7 ± 1.5
BV %PRE	CHF		-2.8 ± 1.4	-7.7 ± 3.0*	-13.3 ± 2.7*	-8.1 ± 4.7*	-6.4 ± 4.3*
	CON		-4.1 ± 2.0*	-8.7 ± 2.7*	-13.1 ± 3.0*	-8.7 ± 2.7*	-4.3 ± 1.4*
PV (ml)	CHF	62.3 ± 6.7	60.8 ± 6.4	60.5 ± 6.6	59.6 ± 5.9	60.2 ± 5.4	61.0 ± 5.9
	CON	59.2 ± 3.3	58.3 ± 3.1	57.2 ± 3.1	56.5 ± 3.4	57.2 ± 3.7	59.1 ± 4.1
PV (ml) %PRE	CHF		-1.2 ± 1.1‡	-5.2 ± 2.1*	-7.9 ± 2.7*	-5.9 ± 3.4*	-5.4 ± 3.6*‡
	CON		-2.7 ± 1.1	-4.1 ± 3.0*	-7.4 ± 3.1*	-5.3 ± 2.7*	-2.1 ± 1.4

Values are mean ± S.D.; *$p \leq 0.05$ vs. Pre-Exercise; ‡ $p \leq 0.05$ vs. CON;
GRP=Group; CHF=chronic heart failure patients; CON=control subjects;
PRE-EX=pre-exercise; 40%HRPK=40%HRpeak; 70%HRPK=70%HRpeak;
PK-EX=peak-exercise; REC-10=10 minute recovery; REC-20=20 minute recovery;
Hct=hematocrit; Hb=hemoglobin; MCHC=mean corpuscular hemoglobin content;
CV=cell volume; BV=blood volume; PV=plasma volume

Mean corpuscular hemoglobin concentrations (MCHC) increased ($p \leq 0.05$ vs. PRE-EX) with corresponding decrease in red cell volumes (CV) ($p \leq 0.05$ vs. PRE-EX) indicating that there was not an extra- to intracellular fluid shift during exercise which might account for changes in PV. These data suggest an exercise intensity-dependent fluid efflux from the vascular compartment (Figure 4.4). The exercise induced hemoconcentration remained significantly elevated in both CHF and CON up to 20 min in recovery ($p \leq 0.05$ vs. PRE-EX).

Digitalis Concentration Responses to Exercise

The exercise-induced fluid efflux from the vascular compartment resulted in an significant increase in serum [digitalis] at 70%HRpeak ($p \leq 0.05$ vs. PRE-EX) and at peak exercise ($p \leq 0.05$ vs. PRE-EX) in the CHF patients (Figure 4.5). Although serum [digitalis] was not significantly altered at low intensity exercise (1.15 ± 0.20 ug•l^{-1} pre-exercise versus 1.05 ± 0.23 ug•l^{-1} at 40%HRpeak), serum [digitalis] increased 15% to 1.30 ± 0.24 ug•l^{-1} at 70%HRpeak ($p \leq 0.05$ vs. PRE-EX) and 29% to 1.39 ± 1.9 ug•l^{-1} at peak exercise ($p \leq 0.05$ vs. PRE-EX).

Neurohumoral Responses to Acute Exercise

Measurements of plasma ANG II, ALDO, AVP, α-ANP, and *B*-ANP were obtained before, immediately after, and 10 minutes in recovery following the SL-GXT and before and immediately after the two submaximal workloads. Based on the relative changes in PV and BV, plasma [neurohormones] were corrected for exercise-induced PV

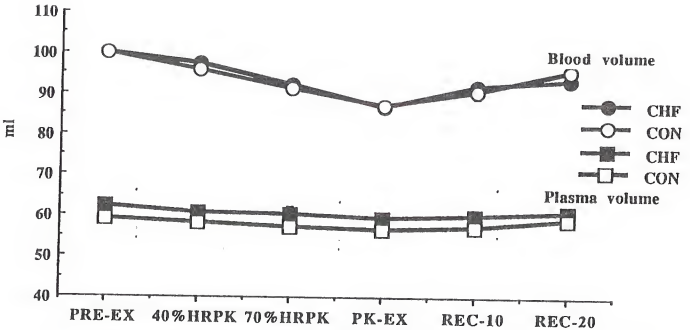

Figure 4.4. Blood volume and plasma volume during and following a graded exercise test in chonic heart failure patients (CHF) and controls (CON).
PRE-EX= prior to exercise; HRPK= heart rate peak; PK-EX= peak exercise;
REC-10= ten minutes in recovery; REC-20= 20 minutes in recovery.

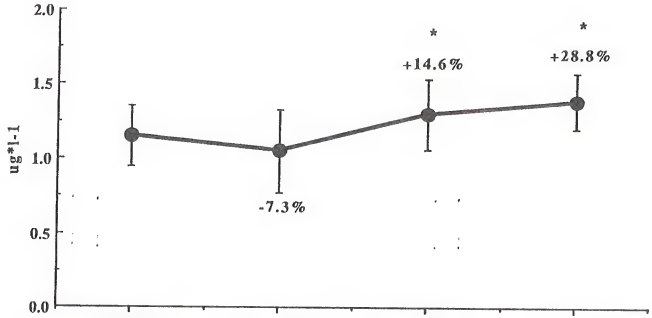

Figure 4.5. Digitalis glycoside concentration during a graded exercise test in chronic heart failure patients. PRE-EX= prior to exercise; HRPK= heart rate peak; PK-EX= peak exercise.
* $p<0.05$ vs. Pre-Exercise.

shifts (Figure 4.1). Plasma [neurohormones] measured during the SL-GXT and submaximal exercise workloads are presented in Table 4.5.

Angiotensin II. Pre-exercise plasma [ANG II] was significantly different ($p \leq 0.05$) between the CHF and CON (4.2±1.6 and 2.1±0.2 pg•ml^{-1}). After correcting for exercise-induced fluid shifts, plasma [ANG II] increased 5% at 40%HRpeak, 7% at 70%HRpeak, and 40% at peak exercise ($p \leq 0.05$ vs. PRE-EX) in the CHF group. In CON, plasma [ANG II] increased 24% at 40%HRpeak, 71% at 70%HRpeak ($p \leq 0.05$ vs. PRE-EX), and 138% at peak exercise ($p \leq 0.05$ vs. PRE-EX). In contrast to basal and low intensity exercise levels, the exercise-induced increases in plasma [ANG II] were not different at 70%HRpeak or at peak-exercise in CON ($p \geq 0.05$; CHF vs. CON). Plasma [ANG II] returned to 4.3±1.5 pg•ml^{-1} and 2.2±0.6 pg•ml^{-1} in CHF and CON, respectively, within 10 minutes in recovery. Comparative changes in plasma [ANG II] for CHF and CON are presented in Figure 4.6.

Aldosterone. Pre-exercise serum [ALDO] was not significantly different ($p \geq 0.05$) between the CHF and CON (328.7±113.4 and 329.6±58.2 pmol•ml^{-1}). After correcting for exercise-induced fluid shifts, serum [ALDO] increased 23% at 40%HRpeak ($p \leq 0.05$ vs. PRE-EX), 32% at 70%HRpeak ($p \leq 0.05$ vs. PRE-EX), and 60% at peak exercise ($p \leq 0.05$ vs. PRE-EX) in the CHF group. In CON, serum [ALDO] increased 15% at 40%HRpeak, 22% at 70%HRpeak ($p \leq 0.05$ vs. PRE-EX), and 50% at peak exercise ($p \leq 0.05$ vs. PRE-EX). The exercise-induced increases in serum [ALDO] were not significantly different between groups during or following exercise ($p \geq 0.05$; CHF vs. CON). Serum [ALDO] remained significantly elevated at 582.9±218.5 pmol•ml^{-1}

Table 4.5. Neurohumoral Responses at Rest, During, and Following Graded Exercise in Chronic Heart Failure Patients and Controls

Variables	GRP	PRE-EX	40%HRPK	70%HRPK	PK-EX	REC-10
ANG II ($pg.ml^{-1}$)	CHF (n=15)	4.2 ± 1.6‡	4.4 ± 1.5‡	4.5 ± 1.6	5.9 ± 2.2*	4.3 ± 1.5‡
	CON (n=9)	2.1 ± 0.2	2.6 ± 0.8	3.6 ± 1.8*	5.0 ± 2.9*	2.2 ± 0.6
ALDO ($pmol.l^{-1}$)	CHF (n=15)	328.7 ± 113.4	405.6 ± 199.6*	435.4 ± 196.1*	525.9 ± 183.2*	582.9 ± 218.5*
	CON (n=9)	329.6 ± 58.2	377.0 ± 116.0	402.5 ± 111.0*	494.7 ± 228.0*	466.2 ± 139.2*
AVP ($pg.ml^{-1}$)	CHF (n=14)	9.1 ± 4.0	14.0 ± 4.6*	18.4 ± 5.3*	19.9 ± 4.9*	14.2 ± 4.6*‡
	CON (n=9)	6.0 ± 4.4	13.9 ± 3.0*	17.9 ± 4.2*	21.0 ± 8.0*	9.7 ± 2.8
α-ANP ($pg.ml^{-1}$)	CHF (n=14)	35.6 ± 11.8‡	63.8 ± 20.8*‡	76.9 ± 19.6*‡	104.4 ± 30.6*‡	96.5 ± 26.2*‡
	CON (n=9)	24.0 ± 7.6	25.9 ± 9.2	44.4 ± 14.3*	61.7 ± 9.0*	41.4 ± 15.8
B-ANP ($pg.ml^{-1}$)	CHF (n=14)	23.2 ± 16.6‡	24.8 ± 7.4‡	45.8 ± 25.6*‡	70.2 ± 41.4*‡	27.2 ± 13.5
	CON (n=9)	3.9 ± 1.8	5.8 ± 2.0	17.2 ± 13.4*	39.2 ± 25.6*	23.7 ± 9.2*

Values are mean ± S.D.; *$p \leq 0.05$ vs. Pre-Exercise; ‡ $p \leq 0.05$ vs. CON;
GRP=Group; CHF=chronic heart failure patients; CON=control subjects;
PRE-EX=pre-exercise; 40%HRPK=40%HRpeak; 70%HRPK=70%HRpeak;
PK-EX=peak-exercise; REC-10=10 minute recovery;
ANG II=Angiotensin II; ALDO=Aldosterone; AVP=Arginine Vasopressin;
α-ANP=α-Atrial Natriuretic Peptide; *B*-ANP=*B*-Atrial Natriuretic Peptide

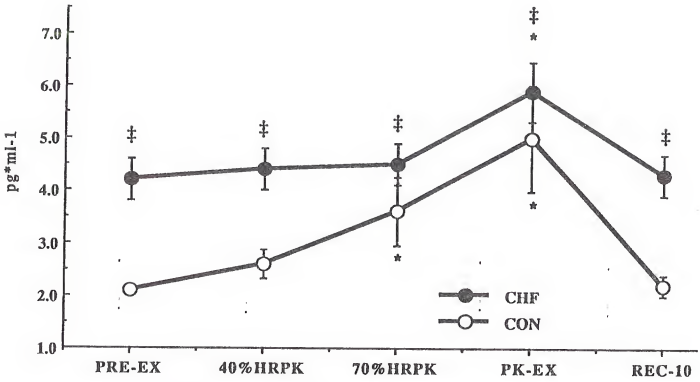

Figure 4.6. Angiotensin II response during and following a graded exercise test in chronic heart failure patients (CHF) and controls (CON).
PRE-EX= prior to exercise; HRPK= heart rate peak; PK-EX= peak exercise; REC-10= ten minutes of recovery
* $p<0.05$ vs. Pre-Exercise; ‡ $p<0.05$ vs. CON.

($p \leq 0.05$ vs. PRE-EX) and 466.2±139.2 pmol•ml^{-1} ($p \leq 0.05$ vs. PRE-EX) in CHF and CON, respectively, at 10 minutes in recovery. Comparative group changes in serum [ALDO] are presented in Figure 4.7.

Arginine Vasopressin. Pre-exercise plasma [AVP] was not significantly different ($p \geq 0.05$) between the CHF and CON (9.1±4.0 and 6.0±4.4 pg•ml^{-1}). After correcting for exercise-induced fluid shifts, plasma [AVP] increased 54% at 40%HRpeak ($p \leq 0.05$ vs. PRE-EX), 102% at 70%HRpeak ($p \leq 0.05$ vs. PRE-EX), and 119% at peak exercise ($p \leq 0.05$ vs. PRE-EX) in the CHF group. In CON, plasma [AVP] increased 132% at 40%HRpeak ($p \leq 0.05$ vs. PRE-EX), 198% at 70%HRpeak ($p \leq 0.05$ vs. PRE-EX), and 250% at peak exercise ($p \leq 0.05$ vs. PRE-EX). The exercise-induced increases in plasma [AVP] were not significantly different between groups during exercise ($p \geq 0.05$; CHF vs. CON). In the CHF group, however, plasma [AVP] remained elevated in recovery ($p \leq 0.05$ vs. PRE-EX) and was significantly greater compared to CON [14.2±4.6 pg•ml^{-1} vs. 9.7±2.8 pg•ml^{-1} for CHF and CON, respectively ($p \leq 0.05$; CHF vs. CON)]. Comparative changes in plasma [AVP] are presented in Figure 4.8.

α-Atrial Natriuretic Peptide. Pre-exercise plasma [α-ANP] were 35.6±11.8 and 24.0±7.6 pg•ml^{-1}, in CHF and CON, respectively, indicating an abnormally high basal level in CHF ($p \leq 0.05$; CHF vs. CON). After correcting for PV shifts, [α-ANP] increased 79% at 40%HRpeak ($p \leq 0.05$ vs. PRE-EX), 116% at 70%HRpeak ($p \leq 0.05$ vs. PRE-EX), and 193% at peak exercise ($p \leq 0.05$ vs. PRE-EX) in the CHF group. In CON, plasma [α-ANP] increased 8% at 40%HRpeak ($p \leq 0.05$ vs. PRE-EX), 85% at 70%HRpeak ($p \leq 0.05$ vs. PRE-EX), and 157% at peak exercise ($p \leq 0.05$ vs. PRE-EX). Plasma [α-

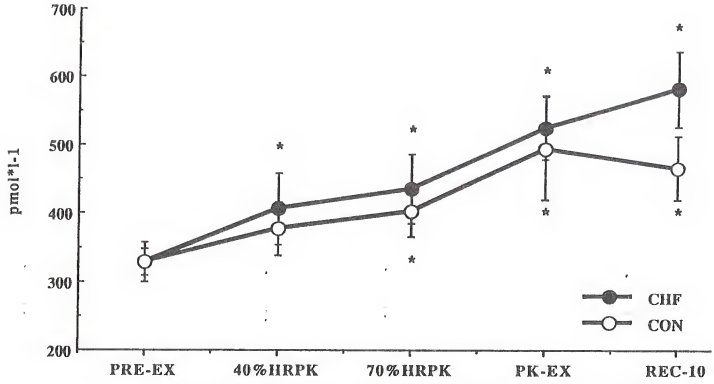

Figure 4.7. Aldosterone response during and following a graded exercise test in chronic heart failure patients (CHF) and controls (CON).
PRE-EX= prior to exercise; HRPK= heart rate peak; PK-EX= peak exercise; REC-10= ten minutes of recovery.
* $p<0.05$ vs. Pre-Exercise.

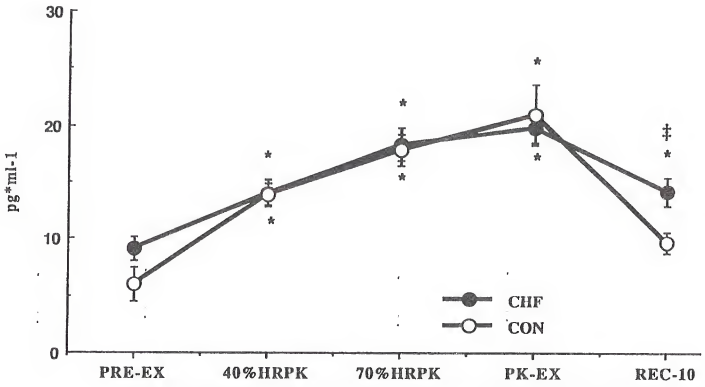

Figure 4.8. Arginine Vasopressin response during and following a graded exercise test in chronic heart failure patients (CHF) and controls (CON).
* $p<0.05$ vs. Pre-Exercise; ‡ $p<0.05$ vs. CON.

ANP] returned to 96.5±26.2 pg•ml^{-1} ($p\leq0.05$ vs. PRE-EX) and 41.4±15.8 pg•ml^{-1} ($p\leq0.05$ vs. PRE-EX), in CHF and CON, respectively, within 10 minutes in recovery. Comparative changes in plasma [α-ANP] for CHF and CON are presented in Figure 4.9.

B-Atrial Natriuretic Peptide. Pre-exercise plasma [*B*-ANP] were 23.2±16.6 and 3.9±1.8 pg•ml^{-1}, in CHF and CON, respectively, indicating an abnormally high basal level in CHF ($p\leq0.05$; CHF vs. CON). After correcting for PV shifts, [*B*-ANP] increased 7% at 40%HRpeak, 97% at 70%HRpeak ($p\leq0.05$ vs. PRE-EX), and 203% at peak exercise ($p\leq0.05$ vs. PRE-EX) in the CHF group. In the CON group, plasma [*B*-ANP] increased 48% at 40%HRpeak, 341% at 70%HRpeak ($p\leq0.05$ vs. PRE-EX), and 905% at peak exercise ($p\leq0.05$ vs. PRE-EX). Plasma [*B*-ANP] returned to 27.2±13.5 pg•ml^{-1} and 23.7±9.2 pg•ml^{-1} ($p\leq0.05$ vs. PRE-EX), in CHF and CON, respectively, within 10 minutes in recovery. Comparative changes in plasma [*B*-ANP] for CHF and CON are presented in Figure 4.10.

Plasma and Blood Volumes

Table 4.6 presents the resting PV and BV data for CHF and CON. Five subjects were not included in this analysis due to potential allergic reactions to the injection and sampling of dye. In contrast to calculated absolute PV and BV, volumes corrected for bodyweight were significantly different between groups ($p\leq0.05$; CHF vs. CON). Relative PV was 34.1±12.9 vs. 44.5±9.0 ml.kg^{-1} and relative BV was 58.5±12.3 vs. 70.8±12.6 ml.kg^{-1} in CHF and CON, respectively. These data suggest that pharmacotherapy, including diuretics and ACE-inhibitors, may contract PV and BV in CHF patients.

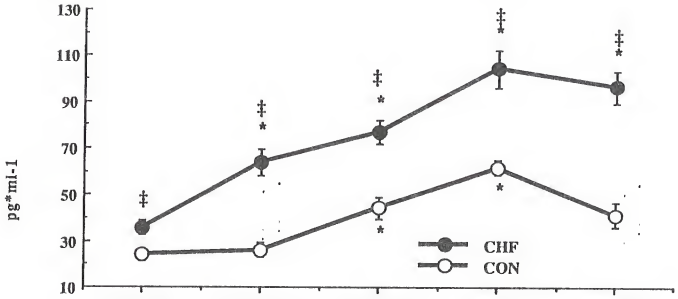

Figure 4.9. Alpha atrial naturetic peptide response during and following a graded exercise test in chronic heart failure patients (CHF) and controls (CON).
PRE-EX= prior to exercise; HRPK= heart rate peak; PK-EX= peak exercise;
REC-10= ten minutes of recovery.
* $p<0.05$ vs. Pre-Exercise; ‡ $p<0.05$ vs. CON.

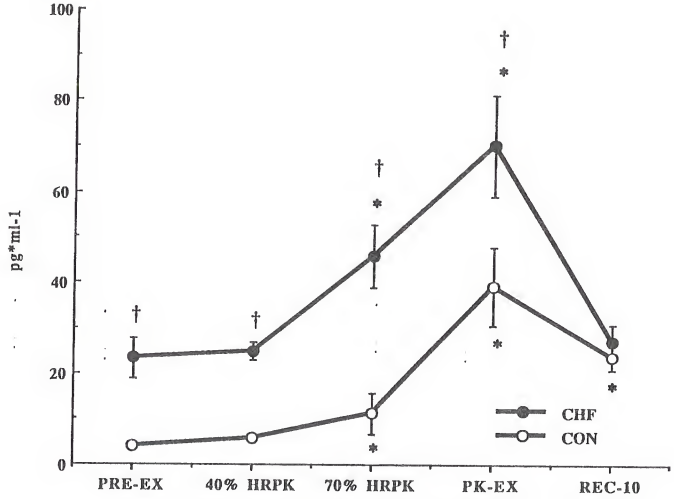

Figure 4.10. Beta naturetic peptide response during and following a graded exercise test in chronic heart failure (CHF) and controls (CON).

PRE-EX= prior to exercise; HRPK= heart rate peak; PK-EX= peak exercise; REC-10= ten minutes of recovery.

* $p<0.05$ vs. PRE-EX; † $p<0.05$ vs. CON.

Table 4.6. Evan's Blue Measurement of Resting Plasma and Blood Volume in Chronic Heart Failure Patients (n=12) and Controls (n=7)		
Variables	Heart Failure Patients	Control Subjects
Hb ($g.dl^{-1}$)	15.5 ± 1.9	16.2 ± 1.4
Hct x 0.91 (%)	36.6 ± 3.5	37.4 ± 1.1
PV (ml)	3489.3 ± 655.0	3728.7 ± 813.2
PV/kg (ml/kg)	34.1 ± 12.9	44.5 ± 9.0‡
BV (ml)	5496.8 ± 1025.4	5942.4 ± 1182.2
BV/kg (ml/kg)	58.5 ± 12.3	70.8 ± 12.6‡

Values are mean ± S.D.; ‡ $p \leq 0.05$ vs. Control Subjects;
Hb=hemoglobin; Hct=hematocrit;
PV=plasma volume; PV/kg=plasma volume / kg bodyweight;
BV=blood volume; BV/kg=blood volume / kg bodyweight

CHAPTER 5
DISCUSSION AND CONCLUSION

Introduction

The present study was designed to evaluate the cardiopulmonary, hemodynamic, and neurohumoral responses to acute exercise in patients with CHF. The results of this study indicated a marked impaired exercise tolerance and capacity as well as an altered neurohormone response to exercise in patients with CHF compared to a group of age-matched healthy controls. In an attempt to provide an explanation of the findings of this study, the discussion will focus on five specific areas including: (1) identifying the unique findings of this study, (2) the potential mechanism which could explain the findings, (3) comparing the results to the existing literature, (4) the limitations of the study, and (5) the clinical implications and future considerations and directions for research.

Paradoxically, most clinical measures of cardiac function [i.e. left ventricular ejection fraction (LVEF)] correlate poorly with the severity of CHF, as defined by exercise tolerance or capacity (Benge et al., 1981; Franciosa et al., 1980; McKirnan et al., 1984). This discordance has led to the identification of multiple compensatory mechanisms which contribute to the marked exercise intolerance (Drexler et al., 1991b, 1992; Kubo et al., 1991; Lipkin et al.,1988; Mancini et al., 1991, 1992; Massie et al., 1988; Sullivan et al., 1995; Zelis et al., 1991). These compensatory mechanisms include: (1) hyperactivation of neurohumoral factors such as increased catecholamines and fluid-

regulatory hormones (Drexler et al., 1991b; Kubo et al., 1991; Zelis et al., 1991), (2) alterations in skeletal muscle blood flow (Drexler et al., 1992; Lipkin et al., 1988; Mancini et al., 1992; Massie et al., 1988; Sullivan et al., 1990), and (3) structural vascular and skeletal muscle changes which impair skeletal muscle metabolism and function (Drexler et al., 1987, 1988, 1992; Zelis et al., 1968, 1970, 1975, 1982, 1991).

Several clinical trials have established the independent prognostic importance of many of the above mentioned peripheral compensatory adaptations to CHF. For example, data from the Department of Veterans Affairs Cooperative Vasodilator-Heart Failure Trials (V-HeFT I and II) identified plasma norepinephrine (NE) as a strong independent predictor of mortality (Cohn et al. 1984, 1992). In the multicenter Scandinavian CONSENSUS trial, patients with high basal levels of angiotensin II (ANG II) and aldosterone (ALDO) had significantly greater rates of mortality (Swedberg et al. 1990, 1992). These data suggested that mortality in CHF may be linked to the activation of the sympathetic nervous system and/or the renin-angiotensin-aldosterone system (RAAS). A similar correlation with mortality has been reported for other fluid regulatory hormones such as vasopressin (AVP) (Benedict et al, 1993; Packer, 1988) and atrial natriuretic peptide (ANP) (Davis et al., 1992; Gottlieb et al. 1989). In addition, exercise capacity, defined by VO_{2peak}, has been identified as a prognostic indicator in CHF (Cohen-Solal & Caviezel, 1994; Cohn & Rector, 1988; Mancini et al., 1991; Parameshwar et al., 1992; Roul et al., 1994; Szlachcic et al., 1985) which should be readily apparent considering that the major determinants of exercise capacity are cardiac output and peripheral oxygen extraction, mechanisms for both of which are affected markedly in CHF.

Although the compensatory adaptations in CHF attempt to maintain cardiac output, arterial pressure, and ultimately perfusion to the vital organs, it is the cyclic magnitude of these compensatory adaptations which leads to end-stage heart failure (Zelis et al., 1991). However, it is not clear to what degree the compensatory adaptations in CHF are inherent to the disease or to other contributing factors such as physical deconditioning and/or malnutrition. Zelis and Flaim (1982) hypothesized that the peripheral adaptations are, in part, protective as they prevent arterial pressure from decreasing when the failing heart cannot adequately increase cardiac output to meet peripheral demands. Others suggest that the peripheral adaptations mimic the deconditioning process seen with prolonged physical inactivity (Adamopoulos & Coats, 1991; Minotti & Dudley, 1993; Stratton et al., 1994; Sullivan et al., 1988). Thus, it is presently not clear to what degree the exercise intolerance in CHF is inherent to the disease itself, the level of inactivity, and/or one or more unidentified contributing factors.

Exercise Capacity and Tolerance

Exercise capacity, as previously mentioned, has considerable prognostic value in patients with CHF (Bittner et al., 1993; Cleland et al., 1987; Cohn & Rector, 1988; Likoff et al., 1987; Mancini et al., 1991; Parameshwar et al., 1992; Roul et al., 1994; Szlachcic et al., 1985). In the study by Szlachcic et al. (1985), patients were followed for 12 months after obtaining VO_{2Peak} measurements during upright cycle ergometry. After 12 months, patients with a VO_{2Peak}<10 $ml.kg^{-1}.min^{-1}$ had significantly higher mortality rates compared with patients with a VO_{2Peak}>10 $ml.kg^{-1}.min^{-1}$. There are several more recent studies that

indicate a significant relationship exists between exercise capacity and survival in CHF patients (Bittner et al., 1993; Cleland et al., 1987; Cohn & Rector, 1988; Likoff et al., 1987; Mancini et al., 1991; Parameshwar et al., 1992; Roul et al., 1994). The results of these studies indicate that the exercise capacity-mortality relationship is independent of cardiac function, clearly represented by the fact that even when LVEF's are similar among CHF patients, those patients with a VO_{2peak}<14 ml.kg^{-1}.min^{-1} have a significantly worse prognosis than those with a VO_{2peak}>14 ml.kg^{-1}.min^{-1}.

In the present study, the mean relative VO_{2peak} (15.0±3.6 ml.kg^{-1}.min^{-1}) was significantly lower in the CHF patients compared to the age-matched healthy individuals (26.0±5.8 ml.kg^{-1}.min^{-1}). These values for exercise capacity are similar to those reported by Szlachcic et al. (1985), Cleland et al. (1987), Likoff et al. (1987), Cohn & Rector (1988), and Roul et al. (1994) indicating a severely impaired exercise capacity. Nine CHF patients participating in the present study had an exercise capacity below 14 ml.kg^{-1}.min^{-1}. In a recent follow-up on CHF patients who participated in a previous study in our laboratory, it was found that six patients who had an impaired exercise capacity of this magnitude had since died, confirming the grave prognosis associated with this disease. Further studies are needed to determine whether exercise training can increase exercise capacity and improve long-term (i.e. >12 months) survivability in CHF patients.

Cardiopulmonary Responses to Exercise in Heart Failure

In the present study, the heart rate and blood pressure response to graded exercise further indicated the decreased cardiac reserve capacity in patients with CHF. The

chronotropic reserve for CHF patients was reduced 72% at 47.8±16.3 beats, compared to 71.8±21.5 beats for the healthy controls. The inability to increase cardiac rate during graded exercise has a detrimental impact on the cardiac output response. Further, the reduction in chronotropic reserve is even more significant for CHF patients considering that the exercise-induced increase in cardiac output is largely dependent on the increase in heart rate, since stroke volume has been shown to decline during exercise (Higginbotham et al., 1986, 1987; Sullivan & Cobb, 1992). A similar observation was noted in the present study for systolic blood pressure (SBP), rate pressure product (RPP), and oxygen pulse (O_2pulse) in CHF patients when compared to healthy controls. These findings are consistent with those previously reported (Cohen-Solal & Caviezel, 1994; Franciosa et al., 1984; Sullivan et al., 1989a; Weber et al., 1982, 1985; Wilson & Mancini, 1993). Although the mechanisms responsible for the reduction in cardiac reserve capacity may be linked to abnormal baroreflex control or downregulation or desensitization of *B*-receptors, it may also reflect the physiological responses to pharmacotherapy (i.e. cardioselective *B*-blockers). Irrespective, the exercise response in CHF in this study was characterized by a narrowing of the reserve capacity of several hemodynamic variables including (1) heart rate, (2) systolic blood pressure, (3) rate pressure product, and (4) O_2pulse. As suggested by previous investigators, the impaired reserve capacity contributes to the exercise intolerance in these patients (Colucci et al., 1989; Feldman et al., 1988; Hammond & Froelicher, 1985; Hanson, 1994; Higginbotham et al., 1983; Jondeau et al., 1992; Weber et al., 1982). The progressive narrowing of the cardiac reserve capacity in CHF appears to be closely related to VO_{2peak} (Weber et al., 1982). Further studies are needed to

determine whether exercise training can increase the cardiac reserve capacity and whether the increase results in reduced morbidity and mortality in CHF patients.

Hemodynamic Responses to Exercise in Heart Failure

This study is the first to report a significant hemoconcentration during the transition from rest to steady-state and non-steady-state exercise in patients with CHF. Although the hemoconcentration reported in this study is similar between the CHF patients and their healthy age-matched counterparts at all exercise intensities assessed, previously reported exercise-induced fluid shift data for healthy young subjects were substantially greater, particularly at the higher exercise intensities (Convertino et al., 1980, 1981; Galbo et al., 1975; Senay et al., 1980; VanBeaumont et al., 1972; 1981; Wilkerson et al., 1977). Plasma volume shifts in young healthy adults have been reported to be approximately 2-4% at 40% VO_{2peak}, 7-10% at 70% VO_{2peak}, and 12-16% at VO_{2peak} (Senay et al., 1985). Although fluid shifts occurred in a similar intensity-dependent manner, the 7.9$\pm$2.7% and 7.4$\pm$3.1% decrease in PV at VO_{2peak} observed in the CHF patients and control subjects, respectively, in the present study are markedly less than the 12-16% decrease at VO_{2peak} reported for healthy young adults. While the fluid shift appears to be dependent on exercise intensity and independent of exercise capacity for all groups assessed, the marked difference between the data collected in the present study and data collected previously on young adults indicates that there may be physiological changes inherent to the aging process which reduce intra- to extravascular fluid shifts during exercise.

It is difficult to compare the findings of this study to prior reports due to methodological differences, as well as differences in data collection techniques. Hagan et al. (1980) concluded that, whenever PV changes are measured, body position, duration of time in that position, and specific time of blood sampling are important factors. In several studies, subject positioning during blood sampling and time between postural changes and when blood samples were drawn varied or were inconsistent or unreported (Costill & Fink, 1974; Senay et al., 1980; VanBeaumont et al., 1981; Wilkerson et al., 1977). Blood samples were collected at either unspecified times and/or with the subject resting in either supine, seated, or standing position. Following or during exercise blood samples were again obtained with the subject in a posture unrelated to the initial posture of the subject or without regard to time in that posture. In the present study, we attempted to minimize the hematologic alterations associated with postural changes by allowing 20 minutes between movement from a supine to standing position, and by standardizing patient posture (standing) as well as the timing of blood sampling relative to the exercise session. Other factors such as the exercise modality, intensity, duration, ambient temperature and humidity, gender, training state, and hydration state have been shown to influence PV during exercise (Senay et al., 1985). The protocol in the present study was standardized in an effort to minimize the effect of these factors.

Due to its inotropic properties, digoxin is one of the most commonly prescribed cardiac glycosides and is considered an essential component of the standard triple therapy regimen for CHF patients. Acute digoxin administration has also been shown to reduce sympatho-excitation, improve peripheral vasodilatation, and normalize baroreflex-

mediated responses in CHF patients (Ferguson, 1992). In contrast to ACE-inhibitors and diuretics, however, digoxin has very narrow dose-response limits and may reach toxic levels resulting in atrial and/or ventricular arrhythmias, conduction defects, electrolyte disturbances, neurological disorders, nausea, and fatigue (Kelly & Smith, 1992). Previously reported research indicates that physical activity increases digoxin binding, particularly to Na^+,K^+- ATPase receptors in skeletal muscle, which produces a substantial lowering (up to 33%) of serum digoxin following exercise in healthy adults (Hall et al., 1989; Jogestrand & Andersson, 1989).

In the present study, serum digoxin levels measured during exercise increased significantly at the higher intensity workloads (1.15 $ug \bullet l^{-1}$ pre-exercise to 1.39 $ug \bullet l^{-1}$ at peak-exercise) in the CHF patients (n=8) but did not approach concentrations considered potentially toxic (>2.5 $ug \bullet l^{-1}$). These data suggest that the exercise-induced increase in plasma digoxin, although significant at the higher intensity workloads, does not warrant concern in these patients. However, recognizing the increasing acceptance of exercise rehabilitation programs for CHF patients, exercise-induced increases in plasma drug concentrations could alter drug efficacy and should be considered when prescribing pharmacotherapy and exercise.

In summary, these results demonstrate that an acute bout of exercise in CHF patients and healthy age-matched subjects induces a $\dot{P}V$ shift from the intra to extravascular compartment averaging 7.0% at peak exercise. Although the plasma shift is dependent upon the exercise intensity, it appears to be independent of exercise capacity. Recognizing that an exercise-induced hemoconcentration increases the plasma

concentration of medications, the results of the present study may have implications in understanding pharmacokinetics and prescribing rehabilitative exercise programs for CHF patients.

Neurohumoral Responses to Acute Exercise in Heart Failure

In the present study, plasma concentrations of ANG II, AVP, ALDO, α-ANP, and *B*-ANP were measured prior to exercise, at two submaximal workloads [(1) 40%HRpeak; (2) 70%HRpeak], at peak exercise, and 10 minutes in recovery following peak exercise. With the exception of α-ANP and *B*-ANP, pre-exercise neurohormone levels in the CHF group remained relatively normal when compared to the healthy subjects. This suggests that standard pharmacotherapy (ACE-inhibitors, digitalis, and diuretics), in addition to physiological compensatory mechanisms, adequately regulates activation of ANG II, ALDO, and AVP in these patients at rest. There are several possible explanations for the elevated plasma α-ANP and *B*-ANP levels prior to exercise, the relative increases in neurohormones during exercise, and the attenuated responses post-exercise considering the fact that neurohumoral adaptations to exercise and changes in PV are complex in healthy persons, much less in CHF patients in which neurohumoral hyperactivation is hallmark. The individual roles of neurohormones are difficult to isolate when integrated whole-body responses to exercise are evaluated as was the case in the present study. The discussion that follows takes into consideration these limitations.

Interestingly, when the resting neurohormone data of the present study are compared to other studies involving CHF patients, there appears to be some discrepancy.

For example, the mean rest supine venous plasma ANP and AVP from the SOLVD trial were 114 [range 54 to 225] $pg \cdot ml^{-1}$ and 2.4 [range 1.9 to 3.5] $pg \cdot ml^{-1}$, respectively in 89 patients with an LVEF less than 45% (Benedict et al., 1993). The mean pre-exercise value for ANP in this study is 220% less and for AVP 279% higher than those reported in the SOLVD-trial. The reasons for the different AVP and ANP values in this study compared to the SOLVD trial are not completely clear, but may be secondary to laboratory differences in the radioimmunoassay procedures, an anticipatory effect prior to physical exertion, and/or obtaining the blood sample in an upright position. The baseline plasma ANG II, ALDO, and ANP levels in the CONSENSUS trial were 72.2 $pg \cdot ml^{-1}$, 1383 $pmol \cdot l^{-1}$, and 463 $pg \cdot ml^{-1}$, respectively, which are significantly higher than presented in this study. However, while it is important to note that all the patients included in the CONSENSUS trial were NYHA class IV and thus severe heart failure, the CONSENSUS trial data clearly depicts the importance of pharmacotherapy and the significant positive relationship between mortality and levels of ANG II ($p<0.05$), ALDO ($p=0.003$), NE ($p<0.001$), epinephrine ($p=0.001$), and ANP ($p=0.003$). Thus, the inter-study differences in neurohumoral concentrations at rest may be affected by several factors including (1) severity, duration and etiology of heart failure, (2) method of blood sampling, (i.e. arterial versus venous, supine versus standing, fasting versus non-fasting) (3) pharmacotherapy, and (4) inter-laboratory radioimmunoassay variability. In contrast to the substantial number of reports providing data on the neurohumoral adaptations to CHF and/or pharmacotherapy in patients at rest, relatively few investigators have studied the neurohumoral responses to acute exercise in this patient population. In the present study, graded exercise resulted in significant increases in ANG II, ALDO, AVP, and α-ANP and

B-ANP in both CHF patients and control subjects, the potential mechanisms of which will be explained in the following sections.

Angiotensin II

Baseline values for plasma ANG II in the present study are similar to those of Aldigier et al. (1991) who reported resting levels in healthy adults of approximately 2 $pg \cdot ml^{-1}$ compared to 6-9 $pg \cdot ml^{-1}$ for patients with CHF. The baseline ANG II levels are also consistent with those reported previously from our laboratory using similar blood sampling and radioimmunassay procedures (Braith et al., 1996) but lower than basal ANG II levels reported for NYHA class III-IV patients (Dzau et al., 1981).

In contrast to previous reports on similar NYHA class CHF patients, however, plasma ANG II did not increase significantly in our patients until peak exercise and not near the magnitude as previously reported from our laboratory. The percent change from pre- to peak -exercise for ANG II were approximately 40% and 138% in the CHF and CON groups, respectively, which are markedly lower for the CHF patients when compared to previous studies (Sigurdsson et al. 1994; Braith et al., 1996). In the study by Sigurdsson et al. (1994), 27 patients on diuretic and ACE-inhibitor (i.e. ramipril) therapy performed an upright cycle exercise test to volitional fatigue or to the onset of significant clinical symptoms. Exercise resulted in an average increase of 100% in plasma ANG II levels. The plasma ANG II concentration difference between the study conducted by Sigurdsson et al. (1994) and the data reported for the present study may be due to the manner in which blood samples were collected and the choice in exercise modality. For example, in the study by Sigurdsson et al. (1994), pre-exercise blood samples were

obtained in the supine position and peak exercise samples in the sitting position. In the present study, all blood samples were obtained in the same position, recognizing that postural shifts may influence hematologic variables as described previously (Costill & Fink, 1974; Hagan et al., 1980; Senay et al., 1980). Taking these factors into consideration, however, does not explain the marked difference between the peak exercise ANG II levels reported in the present study and the plasma ANG II level of 17 $pg \cdot ml^{-1}$ reported previously from our laboratory (Braith et al., 1996). Additional studies are needed to determine the onset kinetics of ANG II during graded submaximal exercise.

In summary, several studies including the present have reported that, despite ACE inhibitor therapy, plasma ANG II levels continue to increase with exercise (Aldigier et al., 1993; Braith et al., 1996; Sigurdsson et al., 1994). Although the exact mechanism(s) for the exercise-induced plasma ANG II increase remain elusive, hyperactivated ACE and enzymes not affected by ACE inhibitors including tonin, cathepsin G, endothelial cell peptidyl dipeptidase, and renal carboxypeptidase may contribute to ANG II formation (Aldigier et al., 1993; Kugler et al., 1982; Sigurdsson et al., 1994).

Aldosterone

In the present study, ALDO increased in an intensity-dependent manner during exercise for both CHF patients and healthy controls to levels observed in similar studies (Aldigier et al., 1993; Nicholls et al., 1992; Sigurdsson et al., 1994). Nicholls et al. (1992) and Sigurdsson et al. (1994) reported a 50% change at peak exercise which is similar to the 60% increase at peak exercise in the present study. Although baseline and maximal exercise-induced serum ALDO levels have been previously reported for CHF patients, this

study is the first to report ALDO responses during graded submaximal exercise and post-exercise for this patient population. Interestingly, there was only an 8% difference between CHF patients and healthy controls at each workload evaluated as ALDO dynamics increased during exercise in a similar manner for both groups. The only difference in ALDO responses between groups participating in the present study was that the post-exercise ALDO levels remained elevated in the CHF group. The marked increase in ALDO at 10 minutes post-exercise follows a similar pattern as and may be attributed to the attenuated post-exercise ANG II response. While the recovery response differed for CHF patients, the similarities in resting and exercise-induced ALDO levels suggests that pharmacotherapy and compensatory physiological mechanisms adequately restored the RAAS to levels comparable with healthy age-matched individuals.

In summary, the role of the RAAS in CHF remains controversial and reported data varies considerably among studies, in part, because of the heterogeneity of the clinical status of the patients studied. In the present study, pre-exercise and exercise-induced increases in ALDO levels were similar for CHF patients and controls. Of more important interest, particularly to the patients enrolled in the present study, was that their pre-exercise ALDO concentrations, which have been shown to have a significant positive relation with mortality ($p=.003$), were approximately one-fourth of those reported for the severe CHF patients studied in the CONSENSUS trials (Swedberg et al., 1990).

Arginine Vasopressin

The resting plasma AVP level reported in the SOLVD trial was 2.4 $pg \cdot ml^{-1}$ which is 279% lower than the baseline AVP of CHF patients in the present study (Benedict et al.,

1993). Creager et al. (1986) also reported a lower resting AVP of 2.4 $pg \cdot ml^{-1}$ in 10 CHF patients with similar physical characteristics. The reason for the difference in plasma AVP levels is not completely clear, but may be secondary to laboratory differences in the radioimmunoassay procedures, an anticipatory effect prior to physical exertion, and/or obtaining the blood sample in an upright versus an recumbent position. The plasma concentrations of AVP observed at rest, 9.1 $pg \cdot ml^{-1}$ and 6.0 $pg \cdot ml^{-1}$ for CHF patients and control individuals in the present study, respectively, were in agreement with those reported in studies evaluating similar subjects (Braith et al., 1996; Goldsmith et al., 1983; 1986; Riegger et al., 1982)

In the present study, graded exercise elicited a dose-response increase in plasma AVP that was significantly greater than baseline for both CHF patients and healthy subjects. These results are similar to those reported previously for healthy individuals that AVP secretion increases during exercise and that the increase is proportional to relative exercise intensity (Convertino et al., 1983; Wade & Claybaugh, 1980). The unique finding in the present study was that, in contrast to the data presented by Kirlin et al. (1986), the magnitude of the AVP response at each exercise intensity was similar to the healthy control subjects. Further, in a pattern similar to ANG II and ALDO, plasma AVP post-exercise remained significantly higher than in the CHF patients compared to the healthy subjects. Although not measured in the present study, PRA, could have been the indirect stimulus for AVP release since a relationship between PRA, ANG II elevations, and increases in plasma AVP have been recorded during exercise (Convertino et al., 1981; Wade & Claybaugh, 1980).

Factors modulating the release of plasma AVP during exercise are not fully understood. Arginine vasopressin secreted in response to dehydration, hemorrhage, or hyperosmolality has a potent vasopressor effect, particularly in animals with baroreceptor denervation, sympathectomy, and nephrectomy (Cowley et al., 1984). While some investigators have suggested that the plasma volume shift mediated hemoconcentration increases plasma osmolality (which stimulates AVP release via hypothalamic receptors) may be the primary stimulus for AVP release during exercise (Convertino et al., 1981), others suggest that non-osmotic factors are dominant in the elevated plasma AVP concentrations present in CHF (Kirlin et al., 1986; Wade & Claybaugh, 1980). Although plasma osmolality was not measured in the present study, previous studies do not suggest a significant difference in osmolality exists between healthy persons and CHF patients during exercise, which is supported in part by the fact that relative plasma volume shifts and increases in plasma AVP concentrations were similar for both groups.

In summary, with the exception of the results reported by Kirlin et al. (1986), we are unaware of any data available describing the AVP response to exercise in CHF patients. The mechanism(s) responsible for the elevated AVP levels in CHF patients at rest and during exercise are not well understood but are believed to be due to non-osmotic causes. Some investigators have speculated that atrial stretch receptors become desensitized with CHF in a similar fashion as arterial baroreceptors, and the reduction in afferent signals normally inhibiting AVP secretion contributes to the elevation of circulating AVP at rest which was also demonstrated by the CHF patients participating in the present study (Cowley et al., 1984; Greenberg et al., 1973; Riegger et al., 1982). The exercise-induced increases in plasma AVP observed in both groups evaluated in the

present study could result from reductions in stroke volume and cardiac output, mediated via cardiac and arterial mechanoreceptors, or from a combination of mechanisms associated with AVP activation (i.e. sympathetic drive, exercise-induced fluid shifts, PRA) (Goldsmith et al., 1983; Sztalowicz et al., 1981).

Atrial Natriuretic Peptides

Although resting and peak-exercise plasma levels of total ANP and α-ANP have been previously reported for CHF patients, the present study is the first to report plasma α-ANP and *B*-ANP responses to graded exercise in this patient population. Several studies have demonstrated that circulating ANP levels are significantly increased in patients with CHF, and ANP has emerged as an important diagnostic and prognostic serum marker (Benedict et al., 1993; Brandt et al., 1993; Burnett et al., 1986; Riegger et al., 1986). Data from the SOLVD trial reported resting values for plasma ANP (total) in healthy adults from 31 to 64 (median value 48) $pg \cdot ml^{-1}$ versus 54 to 225 (median value 114) $pg \cdot ml^{-1}$ for CHF patients (NYHA class II-III) (Benedict et al, 1993). Riegger et al. (1986) reported higher baseline α-ANP values in the range of 57 to 288 $pg \cdot ml^{-1}$ for severe CHF patients (NYHA class III-IV). Although the individual α-ANP data and the total sum of combined α-ANP and *B*-ANP data reported in the present study are lower than data reported in the SOLVD trial, our finding of elevated resting α-ANP is similar in magnitude to other studies using similar blood sampling and radioimmunoassay procedures (Braith et al., 1996). In the present study, resting α-ANP and *B*-ANP levels in the CHF patients were 48% and 495% greater than in the control group, respectively.

The exercise-induced increase in plasma α-ANP concentrations in both CHF and control groups in the present study are similar to those reported previously (Mannix et al., 1990; Saito et al., 1987; Tanaka et al., 1987). Saito et al. (1987) and Tanaka et al. (1987) documented a relationship between exercise intensity and α-ANP levels in healthy individuals, however, their conclusions regarding the onset kinetics of ANP are not consistent. The findings in the present study for healthy adults were similar to the data reported by Saito et al. (1987), who showed that mild exercise (50%HRmax) was associated with a slight increase in plasma α-ANP and high-intensity exercise (85%HRmax) resulted in a 105% increase in circulating α-ANP. In contrast, however, our data at peak exercise is substantially less than the sixfold increase in α-ANP reported by Tanaka et al. (1987). As mentioned previously, however, it is difficult to compare data between laboratories due to differences in blood collection and analysis techniques. In the present study, α-ANP increased 8% at the 40%HRmax workload, 85% at the 70%HRmax workload, and 157% at peak exercise in the healthy individuals. Thus, even though the precise kinetics of ANP production during exercise are not firmly established and there are significant differences reported in the literature, it appears that exercise intensity is a prime factor to consider when exercise is employed to stimulate ANP production.

Several studies have also demonstrated a significant rise in plasma ANP during dynamic exercise in patients with CHF (Donckier et al., 1991; Keller et al., 1988; Nicholls et al., 1992; Petzl et al., 1987; Raine et al., 1986; Sigurdsson et al., 1994). Keller et al. (1988) and Petzl et al. (1987) reported significant increases in plasma ANP during an acute bout of exercise and contributed this rise to increases in left atrial pressure as well as

right atrial distension. Other studies, however, have reported a response comparable to normals (Donckier et al., 1991), or a relatively blunted response, especially in patients with more severe disease (Nicholls et al., 1992; Raine et al., 1986). Although, the blunted response is not clearly understood, it is thought to be the result of cardiac myocyte depletion and/or a mere reflection of the lower exercise levels achieved (Agnoletti et al., 1990). The percent change between rest and peak-exercise exercise in the present study is higher than those reported by Sigurdsson et al. (1994) or Nicholls et al. (1992). The differences between the data presented by Sigurdsson et al. (1994) and the data reported in the present study may again be related to the methodological differences regarding blood sampling and exercise testing. In the study by Nicholls et al. (1992), 28 CHF patients performed a treadmill graded exercise test resulting in a 70% increase in plasma ANP levels at peak exercise. In comparison, plasma α-ANP had already increased 79% at 40%HRpeak in the present study, to 116% at 70%HRpeak, and 193% at peak exercise in the CHF patients. The increases in plasma α-ANP for the CHF patients in the present study were similar in magnitude to those of the healthy subjects, culminating with a threefold increase at peak exercise.

One of the unique findings in the present study is the exercise-induced increase in plasma *B*-ANP in both the healthy controls and CHF patients which, to our knowledge, have not been reported previously. As described above, the less biologically active *B*-ANP accounts for a progressively increasing portion of the total ANP in CHF (Wei et al., 1993). Subsequently, one hypothesis of the present study was that *B*-ANP would account for a progressively increasing proportion of the total ANP released during graded exercise. Unfortunately, our data does not support this hypothesis. While pre-exercise plasma *B*-

ANP levels were approximately sixfold greater in the CHF patients, the relative changes in *B*-ANP at each workload were significantly greater in the control group. When comparing the relative changes, *B*-ANP increased 7% at 40%HRpeak, 97% at 70%HRpeak, and 203% at peak exercise in the CHF group versus increases of 48% at 40%HRpeak, 341% at 70%HRpeak, and 905% at peak exercise in the control group. The relative increase in the less active *B*-ANP in the CHF patients at rest may be the result of the chronic volume and pressure overload and subsequent inability of the atria to synthesize adequate quantities of the active α-ANP. In contrast, the greater relative increases in plasma *B*-ANP accompanying increases in exercise intensity in the healthy subjects indicates that there is a substantial storage capacity of *B*-ANP within the atrial myocytes in healthy individuals which may become depleted in CHF. More research is needed to determine the precise mechanism(s) underlying the increases in plasma α-ANP and B-ANP concentrations during exercise in the both healthy persons and CHF patients.

The parallel increases in ANP and the hormones of the RAAS suggest that there is a dissociation between these systems during exercise and that each may be responding to independent stimuli. Similar to the pathophysiological adaptations associated with CHF, high intensity exercise induces physiological changes which perturb the normal counterbalance relationship between the ANP and RAAS axis (Mannix et al., 1990). Plasma ANP has emerged as an important diagnostic and prognostic marker in CHF and correlates with the functional class of patients, PRA, NE, and mortality (Davis et al., 1992; Gottlieb et al., 1989; Hall et al., 1993). Further, recognizing the relationship between plasma ANP levels (> 125 $pg \cdot ml^{-1}$) and mortality rates, plasma ANP has been identified as a specific and sensitive test to identify asymptomatic patients at risk for CHF

(Hall et al., 1993). Fortunately, none of the patients participating in the present study had plasma ANP levels of this magnitude (> 125 $pg \cdot ml^{-1}$). Considering the potential role of ANP in fluid regulation and edema formation, additional studies are needed to determine the interaction between the relative secretion rates of each ANP subtype and cardiac function during graded exercise.

Plasma and Blood Volumes

Considering that several previous investigators have shown that plasma ANG II, ALDO, and AVP remain elevated in CHF despite pharmacotherapy and that many of our patients had peripheral edema, we hypothesized that circulating plasma and blood volumes would be expanded when compared to a group of healthy age- and weight-matched individuals. The results of our study, however, do not support this hypothesis. Relative plasma volume was 34.1 ± 12.9 versus 44.5 ± 9.0 $ml.kg^{-1}$ and relative blood volume was 58.5 ± 12.3 versus 70.8 ± 12.6 $ml.kg^{-1}$ in the CHF patients and healthy controls, respectively. These data suggest that, in addition to the effects of the natriuretic peptides, standard pharmacotherapy including diuretics and ACE-inhibitors may contract circulating plasma volume and blood volume in CHF patients. Interestingly, in addition to displaying significant peripheral edema, the majority of CHF patients participating in the present study prematurely terminated their maximal exercise test sessions because of a 3+ dyspnea rating which may, in part, reflect pulmonary congestion. The discrepancies between our clinical observations and plasma and blood volume measurements suggest that standard CHF pharmacotherapy may not significantly influence extravascular fluid retention.

Summary and Conclusions

In CHF patients, resting indices may not be representative of abnormal neurohumoral responses which occur during normal daily activities or exercise rehabilitation. Considering the increasing prevalence of exercise rehabilitation being prescribed for this patient population (American Heart Association, 1992; Coats et al., 1992, 1993) and therefore the need to gain a better understanding of the CHF-influenced responses to exercise, we evaluated the temporal pattern of cardiopulmonary, hemodynamic, and neurohumoral activation during graded exercise in 15 CHF patients and compared to nine healthy controls. Data from this study identify several factors which may contribute to the exercise intolerance in CHF: (1) a narrowing of the cardiopulmonary reserve capacity, (2) abnormal activation of several neurohormones involved in fluid regulation and cardiocirculatory control, (3) exercise-induced hemodynamic changes resulting in increased plasma medication concentrations, and (4) pharmacotherapy contracted plasma volume and blood volume.

The first aim of the proposed study was to determine the effects of submaximal and maximal treadmill exercise on several cardiopulmonary variables including heart rate, blood pressure, oxygen consumption, carbon dioxide production, minute ventilation, and oxygen saturation. The hypothesis was that cardiopulmonary variables would be markedly blunted in the CHF patients during submaximal and maximal treadmill exercise. This study demonstrated that the physiologic responses to graded exercise in CHF patients were characterized by a reduction in a number of variables related to cardiopulmonary reserve capacity. Exercise capacity (VO_{2peak}=15.0$\pm$3.6 ml.kg^{-1}.min^{-1}) was markedly

depressed in the CHF group compared to CON (VO_{2peak}= 26.3±5.8 $ml.kg^{-1}.min^{-1}$). The chronotropic reserve during a symptom-limited exercise test was significantly less in heart failure compared to controls (47.8±16.3 versus 71.8±21.5 $beats.min^{-1}$). The exercise responses in the CHF patients were further characterized by a reduction in HR_{peak}, systolic blood pressure, rate pressure product and O_2pulse compared to age- and weight-matched controls. Although, the data from the present study confirms previously reported work in this area, there are also several unique findings which may contribute to a better understanding of the heart failure syndrome.

The second aim of the proposed study was to determine the effects of submaximal and maximal treadmill exercise on intra- to extravascular plasma volume shifts and the hemoconcentration of circulating drugs (e.g. digitalis glycosides). The hypotheses were that graded exercise would result in an intensity-dependent plasma volume shift and an increase in the plasma concentration of prescribed medications. In CHF patients and healthy controls, exercise-induced hydrostatic and oncotic pressure gradients caused an intensity-dependent decrease in plasma and blood volumes and resulted in an significant, but not clinically dangerous, increase in plasma digitalis concentration in the CHF group. Further research needs to evaluate the effects of exercise-induced plasma medications on cardiopulmonary variables, particularly the effect of potentially toxic medications with narrow therapeutic limits on cardiac function.

The third aim of the present study was to determine the effects of acute submaximal and maximal exercise on the neurohumoral responses including ANG II, ALDO, AVP, α-ANP, and *B*-ANP. The hypotheses were that, in contrast to normal resting levels, vasoconstrictor and fluid regulating neurohormones would be markedly

hyperactivated during graded exercise in CHF patients. There was evidence of neurohumoral hyperactivity in the heart failure group prior to exercise. Elevated plasma ANG II, AVP, α–ANP, and *B*-ANP levels indicated that, despite pharmacotherapy, many neurohormones remain hyperactivated at rest in CHF. Although there was further evidence of neurohumoral hyperactivity post-exercise, exercise-induced changes in plasma neurohormones were similar in magnitude between groups. An additional hypothesis supported by the data was that the inactive ANP subtype, *B*-ANP, accounts for a greater proportion of the total circulating ANP at rest and released in response to graded exercise in CHF patients. With the exception of α–ANP and *B*-ANP, these data suggest that compensatory physiological adaptations and pharmacotherapy adequately regulate many of the neurohormones involved in cardiocirculatory control during exercise.

The fourth aim of the proposed study was to determine plasma and blood volumes following standard diuretic and ACE-inhibitor therapy. The hypothesis was that blood volume remains significantly elevated at rest despite standard pharmacotherapy in CHF patients. The data do not support this hypothesis. Relative plasma volume was 34.1±12.9 versus 44.5±9.0 $ml.kg^{-1}$ and relative blood volume was 58.5±12.3 versus 70.8±12.6 $ml.kg^{-1}$ in the CHF patients and healthy controls, respectively. These data suggest that, in addition to the effects of the natriuretic peptides, standard pharmacotherapy including diuretics and ACE-inhibitors may contract circulating plasma volume and blood volume in CHF patients.

In summary, these findings demonstrate that an exercise test may be useful in identifying underlying cardiopulmonary, hemodynamic, and neurohumoral abnormalities associated with heart failure. In addition to contributing to the marked reduction in

cardiopulmonary and neurohumoral reserve, the compensatory adaptations associated with the heart failure syndrome and standard pharmacotherapy regimen prescribed to CHF patients may also contract circulating plasma and blood volume, the compounding effect of these factors contributing to the marked exercise intolerance exhibited by this patient population. The exercise-induced increase in circulating plasma digitalis may provide further justification for close monitoring of CHF patients participating in exercise rehabilitation programs, particularly those on high doses of pharmacotherapy.

Clinical Implications

Heart failure is at present the nation's most rapidly growing cardiovascular disorder and is a major cause of morbidity and mortality. Heart failure is a syndrome in which a reduction in cardiac function results in a series of time-dependent compensatory adaptations. Although, these compensatory changes are often remarkably effective in normalizing cardiocirculatory function, they exact a price which results in a marked inability of patients to carry out activities of daily living, care for themselves, and support their families. The major emphasis of the present study was to determine the manner in which the compensatory adaptations to CHF change during an acute bout of exercise. Unfortunately, these same compensatory adaptations which stabilize cardiocirculatory variables and subsequently peripheral perfusion at rest, result in reductions in exercise capacity and tolerance. It is this apparent paradox which seriously complicates the treatment and management of the CHF patient.

Future studies will have to determine the effect of varying pharmacotherapy regimens and exercise training on cardiopulmonary, hemodynamic, and neurohumoral variables, particularly those associated with increased morbidity and mortality in CHF. The results of these types of studies could provide insight into the development of more effective treatment strategies to protect the compensatory adaptations aimed at optimizing cardiocirculatory performance, yet delay the maladaptive processes which lead to a decompensated state or even end-stage heart failure. Understanding the key controllers and signal systems which contribute to the heart failure syndrome will ultimately result in the development of improved treatment strategies for this disease.

Optimal management of patients with CHF requires an understanding of the role of the many compensatory pathophysiological adaptations contributing to the exercise intolerance and chronic fatigue. The clinical contribution of the present study was to provide further insight into the physiological responses that occur during the transition from rest to steady-state and non-steady state exercise in patients with CHF. Such information could provide the clinician with an opportunity to determine a more optimal treatment strategy, particularly for those patients enrolled in exercise rehabilitation programs. The finding that several plasma neurohormones were markedly different than control subjects suggests that current pharmacotherapy alone may not be an adequate treatment strategy in these patients. Recognizing that neurohumoral hyperactivity carries an ominous prognosis suggests that more aggressive pharmacotherapy therapy may be needed to significantly reduce morbidity and mortality and increase functional capacity in patients with heart failure.

APPENDIX A
INSTITUTIONAL REVIEW BOARD APPROVAL LETTER

UNIVERSITY OF FLORIDA

Health Center Institutional Review Board

PO Box 100173
Gainesville, FL 32610-0173
(352) 846-1494
Telefax: (352) 846-1497

Principal Investigator: BRAITH, RANDY W.
Address: BOX 118206

IRB PROJECT # 126-96
EXPIRES 04/16/97

CARDIOPULMONARY, HEMODYNAMIC, AND NEUROENDOCRINE RESPONSES TO ACUTE EXERCISE IN PATIENTS WITH CHRONIC HEART FAILURE

Approval of this research project (including the Informed Consent Form and Protocol) was granted on 04/16/96. Enclosed is the dated, IRB-approved Informed Consent Form that must be used for enrolling subjects into this protocol. Three months before expiration, you will be reminded to inform the IRB of the status of this project. Reapproval must be granted before the expiration date or the project will be automatically 'suspended'.

Changes in the research may not be initiated without IRB review and approval except where necessary to eliminate hazards to human subjects. Any changes which have been necessary for the above reasons must be promptly reported to the IRB.

The Principal Investigator must report to the Chair of the IRB within 5 days, in writing, any unanticipated problems involving risks to the subjects or others, such as adverse reactions to biological drugs, radio-isotopes or to medical devices. Records pertaining to research must be retained for at least three years after completion of the research.

If it is anticipated that VA patients will be included in this project, or if the project is to be conducted in part on VA premises or performed by a VA employee during VA-compensated time, final approval should be obtained by application to the VA Hospital Research Office.

You are responsible for notifying all parties about the approval of this project, including your Co-PIs and Department Chair. If you have any questions, please feel free to contact Barbara Frentzen, IRB Coordinator, at (352) 846-1494.

David T. Lowenthal, MD, PhD
Chair, IRB-01

cc: IRB File; Division of Sponsored Research; Rhonda Cooper, Pharmacy; Edward Block, VA; Sandra Barnawell, CRC

APPENDIX B
DEMOGRAPHIC, MEDICAL, AND ACTIVITY QUESTIONNAIRES

Investigator:	Site:	Protocol:	Form:
	Univ. of Florida		CHX.

CARDIAC HISTORY

Subject's Initials:	Subject's Code #:	Date Performed:

Cardiac Failure Classification (NYHA)

Class I II III IV

(Circle One)

New York Heart Association

Classification of Heart Failure

Class I: No Symptoms

Class II: Symptoms with ordinary activity

Class III: Symptoms with less than ordinary activity

Class IV: Symptoms at rest

Angina Pectoris Classification

Class I II III IV

(Circle One)

Canadian Cardiovasc. Society's

Classification of Angina Pectoris

Class I: AP with strenous, rapid or prolonged exertion

Class II: Slight limitation of ordinary activity

Class III: Marked limitation of ordinary activity

Class IV: Inability to carry on any physical activity w/o discomfort

Cardiac Findings	**YES**	**NO**
A. Left Ventricular Heave		
B. Atrial Gallops		
C. Protodiastolic Gallop		
D. Normal Rhythm		
E. Jugular Venous Disten.		
F. Pulmonary Rales		
G. Normal Arterial Pulse		
H. Systolic Murmur		
I. Other_____		

Cardiac Status:

A. Uncompromised	
B. Slightly	
C. Moderately	
D. Severely	

Prognosis:

A. Good	
B. Good with Rx	
C. Fair with Rx	
D. Guarded with Rx	

ECG: Normal Abnormal

Cardio:Thoracic Ratio

Diagnosis:

Other Non-Cardiac Diagnosis:

Investigator's Signature: Date:

Investigator: Protocol: Form:

MEDICAL HISTORY

Subject's Initials: Subject's Code #: Date Performed:

Condition	Check YES	NO	Unknown	If Yes, Please Give Details
1. Emotional Disorder				
2. CNS Disorder				
3. EENT Disorder				
4. CV. Disorder				
5. Resp. Disorder				
6. Hepatic Disorder				
7. Dermatologic Disorder				
8. Musculoskeletal Disorder				
9. Endocrine-Metabolic Disorder				
10. GI Disorder				
11. Hematopoetic/Lymph Disorder				
12. Renal-Genitourinary Disorder				
13. Allergies/Drug Sensitivities				
14. Major Surgeries				
15. Alcohol Abuse				
16. Drug Abuse				
17. Daily Tobacco Use				
18. Malignancy				
19. Other				

Comments:

Investigator's Signature: Date

Investigator:

Site: Univ. of Florida

Protocol:

Form: MED.

CONCURRENT MEDICATIONS

Subject's Initials:

Subject's Code #:

Date Performed:

Drug Name	Dose	Frequency	Date Started	Date Stopped	Comments

Investigator:	Site:	Protocol:	Form:
	Univ. of Florida		**RBPHR**

RESTING BLOOD PRESSURE / HEART RATE

Subject's Initials:	Subject's Code #:	Date Performed

	T1	T2	T3
Blood Pressure			
1			
2			
3			
Heart Rate			
1			
2			
3			

Time: **(at measurement)**			
Date:			

TESTER			

Comments:

Investigator:	Site:	Protocol:	Form:
	Univ. of Florida		**I/E**

INCLUSION/EXCLUSION CRITERIA

Subject's Initials: Subject's Code #: Date:

Inclusion Criteria	Y	N
1. Has patient read and signed informed consent?		
2. Is patient 18 yrs or older?		
3. Is the left vent. ejection fraction (LVEF) <40%?		
4. Is the etiology of CHF, ischemic heart disease?		
5. Is the patient in NYHA functional class II or III? Which one? II ___ III ___		
6. Does the patient have CAD as documented by history of MI and/or catheterization ?		
Exclusion Criteria	Y	N
1. Did the patient have a myocardial infarct in the last 4 weeks?		
2. Has the patient had acute unstable ischemia and/or angina in the past 4 weeks?		
3. Does the patient have significant other non-cardiac diseases (uncontrolled hypertension, COPD, orthopedic problems)?		
4. Does the patient have a cardiac pacemaker, AICD, or metal implant?		
5. Is the patient currently participating in any other clinical trials or has he participated in one in the last 30 days?		

The patient meets all entrance criteria and is qualified to participate in the study.

Investigator's signature: _____ Date: _____

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GAINESVILLE, FL 32611
904-392-9575

DEMOGRAPHIC INFORMATION

NAME_____ DATE_____/_____/_____
Last First MI Month Day Year

AGE_____ DATE OF BIRTH _____/_____/_____
Month Day Year

SOCIAL SECURITY #_____-___-_____ PHONE #_____

HEIGHT _____ in___ cm___

WEIGHT _____ lb___ kg___

RESIDENCE _____
Street

_____
City State Zip Country

REFERRING PHYSICIAN _____

SURGEON (if applicable) _____

HOME PHYSICIAN (if different from Referring M.D.)_____

ADDRESS _____
Street

_____
City State Zip Country

Sex ___ Male ___ Female

Race ___ White ___ Black ___ Asian ___ Hispanic ___ Other:

Marital Status
___ Single
___ Married # years:_____
___ Divorced or separated # years:_____
___ Widowed # years:_____

Demographic Information (Page 2)

RELIGION (optional)

___ Catholic
___ Protestant
___ Jewish
___ Jehovah Witness
___ Hindu
___ Muslim
___ None
___ Other: _____

EDUCATION COMPLETED

___ 1-8 years
___ 9-12 years
___ 13-16 years
___ 17-18 years
___ More than 18 years
___ High School Graduate
___ Bachelor's degree
___ Master's degree
___ Doctoral degree

OCCUPATION (list) _____

PRESENT WORK STATUS

___ Working full time
___ Working part time
___ Not employed - Reason: ___ Medical ___ Other
___ Retired

INDICATE YOUR FAMILY INCOME BEFORE TAXES (U.S. dollar equivalent)

___ Less than $10,000
___ $10,000 - $25,000
___ $25,000 - $50,000
___ More than $50,000

STATEMENT OF CONFIDENTIALITY

I understand that information contained on this questionnaire is regarded as confidential, and will not be released without my prior written permission. The information will not be used for the setting of fees. The Center for Exercise Science may, however, use the information for statistical and other research purposes.

_____ _____
Signature Date

CENTER FOR EXERCISE SCIENCE
UNIVERSITY OF FLORIDA, RM 27 FLG
GAINESVILLE, FL 32611
904-392-9575

NAME_____ ID#_____

CARDIOVASCULAR HISTORY

Answer the following questions, indicating the month and year of the event of diagnosis where appropriate.

		Yes	No	Month/Year
1.	Has a doctor ever told you that you have heart disease?	___	___	____/____
2.	Have your ever had a heart attack?	___	___	____/____

If more than one heart attack, list date(s):

____/____ ____/____ ____/____
mo yr mo yr mo yr

3. Have you had coronary artery bypass graft surgery? ___ ___

If yes, list date(s) and # of grafts: ____/____ # grafts: ___1 ___2 ___3 ___4+
mo yr

____/____ # grafts: ___1 ___2 ___3 ___4+
mo yr

____/____ # grafts: ___1 ___2 ___3 ___4+
mo yr

4. Have you ever had a stroke? ___ ___ ____/____

If more than one stroke,

____/____ ____/____ ____/____
mo yr mo yr mo yr

Cardiovascular History (Page 2)	Yes	No	Month/Year
5. Do you have high blood pressure?	___	___	____/____

If yes, how long have you had high blood pressure (hypertension)?

_____ less than 1 year
_____ 1-5 years
_____ 6-10 years
_____ more than 10 years

6. Do you have diabetes mellitus	___	___	____/____
7. Do you take insulin for diabetes?	___	___	

If yes, how long have you taken insulin?

___ less than 1 year
___ 1-5 years
___ 6-10 years
___ more than 10 years

8. Do you take oral hypoglycemics for diabetes?	___	___	
9. Do you have a cardiac pacemaker?	___	___	

If yes, how long have you had a cardiac pacemaker?

___ less than 1 year
___ 1-5 years
___ 6-10 years
___ more than 10 years

10. Have you had a carotid endarterectomy?	___	___	
11. Has your doctor ever told you that you have a heart valve problem?	___	___	____/____
12. Have you had heart valves replacement surgery?	___	___	____/____

If yes, what heart valves were replaced? ___ mitral ___ aortic

13. Have you had cardiomyopathy?	___	___	____/____
14. Have you had a heart aneurysm?	___	___	____/____

Cardiovascular History (Page 3)	Yes	No	Month/Year
15. Have you had heart failure?	___	___	____/____
16. Have you ever had a cardiac arrest?	___	___	____/____

17. OTHER MEDICAL PROBLEMS: Indicate if you have had any of the following:

Past	Now	
____	____	Alcoholism
____	____	Allergies
____	____	Anemia
____	____	Arthritis
____	____	Asthma
____	____	Back injury or problem
____	____	Blood clots
____	____	Bronchitis
____	____	Cirrhosis
____	____	Claudication
____	____	Elbow or shoulder problems
____	____	Emotional disorder
____	____	Eye problems
____	____	Gall bladder disease
____	____	Glaucoma
____	____	Gout
____	____	Headaches
____	____	Hemorrhoids
____	____	Hernia
____	____	Hip, knee or ankle problems
____	____	Intestinal disorders
____	____	Kidney disease
____	____	Liver disease
____	____	Lung disease
____	____	Mental illness
____	____	Neurologic disorder
____	____	OB/GYN problems
____	____	Obesity/overweight
____	____	Prostate trouble
____	____	Rheumatic fever
____	____	Seizure disorder
____	____	Stomach disease
____	____	Thyroid disease
____	____	Tumors or cancer - List type:_____
____	____	Ulcers
____	____	Other - specify:_____

Cardiovascular History (Page 4)

18. SURGICAL PROCEDURES:

Yes	No	Month/Year	
____	____	____/____	Appendectomy
____	____	____/____	Back surgery
____	____	____/____	Bladder surgery
____	____	____/____	Bowel surgery
____	____	____/____	Breast surgery
____	____	____/____	Cataract surgery
____	____	____/____	Gall bladder surgery
____	____	____/____	Hemorrhoid surgery
____	____	____/____	Joint surgery
____	____	____/____	Kidney surgery
____	____	____/____	Lung surgery
____	____	____/____	OB/GYN surgery
____	____	____/____	Prostate surgery
____	____	____/____	Stomach surgery

Other - specify:_____

19. MEDICATIONS: Indicate the medicines you currently use on a regular basis.

Yes	No		Yes	No	
___	___	Allergy medicines/antihistamines			
___	___	Antacids			
___	___	Antibiotics			
___	___	Anti-arrhythmics			
___	___	Anti-inflammatory agents			
___	___	Aspirin			
___	___	Asthma medicines			
___	___	Beta blockers			
___	___	Birth control pills (# of years: __0-1 __1-5 __5-10 __10+)			
___	___	Blood pressure medicines			
___	___	Blood thinners			
___	___	Cortisone			
___	___	Diabetes medicines/insulin			
___	___	Diuretics/"water pills"			
___	___	Gout medicines			
___	___	Heart medicines			
___	___	Hormones/estrogen	___	___	Seizure medicines
___	___	Laxatives	___	___	Thyroid medicines
___	___	Nitroglycerin	___	___	Tranquilizers
___	___	Pain medicines	___	___	Vitamins / iron
___	___	Psychiatric meds/anti-depressants			
___	___	Sedatives/sleeping pills			

Other - specify:_____

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NAME_____ ID#_____ DATE_____

FAMILY HEALTH HISTORY

A. If any members of your immediate family have or have had any of the following conditions, indicate their age at the time of the event:

	Father	Mother	Brother	Sister
Heart Attack	___yr	___yr	___yr	___yr
Stroke	___yr	___yr	___yr	___yr
Coronary Artery Disease	___yr	___yr	___yr	___yr
If deceased, note age at time of death	___yr	___yr	___yr	___yr

B. Indicate if any members of your immediate family have or have had the following conditions by marking the appropriate lines.

	Father	Mother	Brother	Sister
High Blood Pressure	___yr	___yr	___yr	___yr
High Cholesterol	___yr	___yr	___yr	___yr
Diabetes	___yr	___yr	___yr	___yr
Obesity	___yr	___yr	___yr	___yr

NAME_____ ID#_____ DATE_____

ACTIVITY STATUS

1. Please indicate your usual activities.

	Frequency per month					Minutes per session			
	1-4	5-8	9-12	3-16	17+	0-20	20-40	40-60	60+
__ Badminton	___	___	___	___	___	___	___	___	___
__ Baseball / Softball	___	___	___	___	___	___	___	___	___
__ Boating	___	___	___	___	___	___	___	___	___
__ Bowling	___	___	___	___	___	___	___	___	___
__ Cycling (motor)	___	___	___	___	___	___	___	___	___
__ Cycling (road)	___	___	___	___	___	___	___	___	___
__ Badminton (stationary)	___	___	___	___	___	___	___	___	___
__ Dance (aerobic)	___	___	___	___	___	___	___	___	___
__ Dance (social)	___	___	___	___	___	___	___	___	___
__ Golf (ride)	___	___	___	___	___	___	___	___	___
__ Golf (walk)	___	___	___	___	___	___	___	___	___
__ Gymnastics	___	___	___	___	___	___	___	___	___
__ Hiking	___	___	___	___	___	___	___	___	___
__ Horseback Riding	___	___	___	___	___	___	___	___	___
__ Hunting / Fishing	___	___	___	___	___	___	___	___	___
__ Jogging / Running	___	___	___	___	___	___	___	___	___
__ Martial Arts	___	___	___	___	___	___	___	___	___
__ Racquetball / Handball	___	___	___	___	___	___	___	___	___
__ Rope Jumping	___	___	___	___	___	___	___	___	___
__ Rowing / Canoeing	___	___	___	___	___	___	___	___	___
__ Skating	___	___	___	___	___	___	___	___	___
__ Skiing (cross ctry)	___	___	___	___	___	___	___	___	___
__ Skiing (water)	___	___	___	___	___	___	___	___	___
__ Soccer / Football	___	___	___	___	___	___	___	___	___
__ Swimming	___	___	___	___	___	___	___	___	___
__ Table Tennis	___	___	___	___	___	___	___	___	___
__ Tennis	___	___	___	___	___	___	___	___	___
__ Volleyball	___	___	___	___	___	___	___	___	___
__ Walking	___	___	___	___	___	___	___	___	___
__ Weight Training	___	___	___	___	___	___	___	___	___
__ Yardwork / Gardening	___	___	___	___	___	___	___	___	___
__ Other - specify:									

2. Does your usual job require sustained physical activity?
___ Yes ___ No ___ Not employed ___ Not applicable (retired)
3. How would you rate your physical fitness (endurance)? low medium high
4. How would you rate your strength? low medium high

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904-392-9575

NAME_____ ID#_____ DATE_____

TOBACCO HISTORY

1. Have you ever used any tobacco product on a regular basis?

___ Yes ___ No

IF YES: Continue IF NO: Go on to next section

2. What form(s) of tobacco do/did you regularly use?

Past	Now		# years	Amount/Day
___	___	Cigarettes	_____	____ packs
___	___	Cigars	_____	____ cigars
___	___	Pipe	_____	____ pipefuls
___	___	Chewing tobacco	_____	____ chaws
___	___	Snuff	_____	____ dips

3. Are you a former cigarette smoker?

___ Yes ___ No

IF YES:

a. How long ago did you stop smoking?

___ less than 6 months ___ 3-5 years
___ 6-12 months ___ 5-10 years
___ 1-2 years ___ more than 10 years

b. What was your reason for stopping?

___ Doctor's advice
___ Concern about health
___ Heart surgery or cardiac event
___ Family pressure
___ Education program
___ Other - specify: _____

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NAME_____ ID#_____ DATE_____

NUTRITION

	Yes	No
1. Do you follow any of the following restrictive diets for medical reasons?		
diabetic	___	___
low cholesterol/low fat	___	___
low sodium or salt free	___	___
renal	___	___
ulcer or bland	___	___
weight reduction	___	___
gastric banding	___	___
kosher	___	___
vegetarian	___	___
other (specify:_____)		
2. Do you deliberately avoid any foods? If yes, specify:_____	___	___
3. Do you have any of the following problems?		
nausea	___	___
vomiting	___	___
diarrhea	___	___
constipation	___	___
4. Do you regularly take vitamins or minerals?	___	___
5. Has your food intake increased lately?	___	___
6. Has your food intake decreased lately?	___	___
7. Has your weight increased recently? If yes, specify amount:___lb	___	___

8. Has your weight decreased recently? If yes, specify amount:___lb

9. What is your current weight? ___lb 10. What is your height? ___in

11. What did you weigh at age 20? ___lb 30 ___lb 40 ___lb 50 ___lb 60 ___lb

12. What would you like to weigh? ___lb

Nutrition (Page 2)

Using the scale provided, indicate your response by checking the appropriate box:

SCALE	never	occasionally	frequently	always

13. How often do you prepare meat, poultry and fish in the following ways:

baked or roasted	___	___	___	___
fried	___	___	___	___
deep-fat fried	___	___	___	___
broiled	___	___	___	___
steamed (boiled)	___	___	___	___

14. How often do you use cooking/table fats?

butter, lard, shortening	___	___	___	___
margarine, vegetable oils	___	___	___	___

15. How often do you salt your food during preparation?

	___	___	___	___

16. How often do you salt your food at the table?

	___	___	___	___

17. Indicate how often you consume the following:

Alcohol	___	___	___	___
Bread, cereal, rice, potatoes	___	___	___	___
Desserts	___	___	___	___
Eggs	___	___	___	___
Fruits	___	___	___	___
Meat, poultry, fish	___	___	___	___
Milk -< 2%	___	___	___	___
Milk-whole	___	___	___	___
Soft drinks with sugar	___	___	___	___

Nutrition (Page 3)

SCALE	never	occasionally	frequently	always
Snacks	___	___	___	___
Sugar	___	___	___	___
Vegetables	___	___	___	___

18. How many cups of caffeinated coffee, tea or cola drinks do you drink each day?

___ less than 3 cups
___ 3-6 cups
___ 7-10 cups
___ more than 10 cups

CENTER FOR EXERCISE SCIENCE
UNIVERSITY OF FLORIDA, RM 27 FLG
GAINESVILLE, FL 32611
904-392-9575

NAME_____ ID#_____ DATE_____

STRESS SURVEY

A. For each of the scales below, check the number that best any describes how you generally feel.

1.	___1	___2	___3	___4	___5
	NEVER WORRY	RARELY WORRY	SOMETIMES WORRY	OFTEN WORRY	ALWAYS WORRY
2.	___1	___2	___3	___4	___5
	NEVER TENSE	RARELY TENSE	SOMETIMES TENSE	OFTEN TENSE	ALWAYS TENSE
3.	___1	___2	___3	___4	___5
	NEVER ANGRY	RARELY ANGRY	SOMETIMES ANGRY	OFTEN ANGRY	ALWAYS ANGRY

B. What things most often cause you to worry or be tense?

___Work ___Health problems ___Money
___Family matters ___Time pressures ___Other_____

C. Think back on each possible life event listed below, and decide if it happened to you within the last year. If the event did happen, check the box next to it.

		Yes	No
1.	A lot more or a lot less troule with the boss	___	___
2.	A major change in sleeping habits (sleeping a lot more or a lot less)	___	___
3.	A major change in eating habits (a lot more or a lot less food intake, or different meal hours)	___	___
4.	A revision of personal habits (dress, manners, associations, etc.)	___	___
5.	A major change in your usual type and/or amount of recreation.	___	___
6.	A major change in your social activities (clubs,dancing, visiting, etc.)	___	___
7.	A major change in church activities (a lot more / less than usual.)	___	___
8.	A major change in number of family get-togethers.	___	___
9.	A major change in financial state (a lot worse off or a lot better off)	___	___
10.	In-law troubles.	___	___
11.	A major change in the number of arguments with spouse	___	___
12.	Sexual difficulties.	___	___

Stress Survey (Page 2)

D. In the space provided, indicate the number of times that each applicable event happened to you within the last two years.

		Yes	No	# x's
1.	Major personal injury or illness	___	___	___
2.	Death of close family member (other than spouse.)	___	___	___
3.	Death of spouse.	___	___	___
4.	Death of close friend.	___	___	___
5.	Gaining a new family member (through birth, adoption, oldster moving in, etc.)	___	___	___
6.	Major change in the health / behavior of a family member.	___	___	___
7.	Change in residence.	___	___	___
8.	Detention in jail or other institution.	___	___	___
9.	Minor violations of the law (traffic tickets, jaywalking, disturbing the peace, etc.)	___	___	___
10.	Major business readjustment (merger, reorganization, bankruptcy, etc.)	___	___	___
11.	Marriage.	___	___	___
12.	Divorce.	___	___	___
13.	Marital separation from spouse.	___	___	___
14.	Outstanding personal achievement.	___	___	___
15.	Son or daughter leaving home (marriage, attending college, etc.)	___	___	___
16.	Retirement from work.	___	___	___
17.	Major change in working hours or conditions.	___	___	___
18.	Major change in responsibilities at work.	___	___	___
19.	Being fired from work.	___	___	___
20.	Major change in living conditions (building a new home, remodeling, deterioration of home or neighborhood.)	___	___	___
21.	Wife beginning or ceasing work outside the home.	___	___	___
22.	Taking on a mortgage greater than $10,000 (purchasing a home, business, etc.)	___	___	___
23.	Taking on a mortgage or loan.	___	___	___
24.	Foreclosure on a mortgage or loan.	___	___	___
25.	Vacation.	___	___	___
26.	Changing to a new school.	___	___	___
27.	Changing to a different line of work.	___	___	___
28.	Beginning or ceasing formal schooling.	___	___	___
29.	Marital reconciliation with mate.	___	___	___
30.	Pregnancy.	___	___	___

APPENDIX C
INFORMED CONSENT TO PARTICIPATE IN RESEARCH

IRB# 126-96

Informed Consent to Participate in Research

J. Hillis Miller Health Center
University of Florida
Gainesville, Florida 32610

You are being invited to participate in a research study. This form is designed to provide you with information about the study. The Principal Investigator or representative will describe this study to you and answer any of your questions. If you have any questions or complaints about the informed consent process or the research study, please contact the Institutional Review Board (IRB), the committee that protects human subjects, at (352) 846-1494.

1. Name of Subject

2. Title of Research Study

Cardiopulmonary, Hemodynamic, and Neuroendocrine Responses to Acute Exercise in Patients with Chronic Heart Failure

3. a. Principal Investigator(s) and Telephone Number(s)

Randy W. Braith, Ph.D. (352) 392-9575
Michael L. Pollock, Ph.D. (352) 392-9575

Co-Investigator(s)

Matthew S. Feigenbaum, M.Ed.
Michael A. Welsch, M.S.
Carl J. Pepine, M.D.
Phillip Posner. Ph.D.
Charles Williams, Ed.D.

b. Sponsor of the Study (if any)

None

4. The Purpose of the Research

The purpose of this study is to examine the differences in fluid-regulating hormone concentrations, total blood volume, and the volume of blood pumped by the heart during exercise between heart failure patients and healthy individuals.

5. Procedures for This Research

You are being asked to participate in a study which will involve four visits to the Center for Exercise Science over the period of three weeks.

The first visit will be an orientation and practice. You will receive a full explanation of the study along with its benefits and risks. You will be asked to read and sign an informed consent and complete a medical history and exercise activity questionnaire. It is very important that you be completely honest about any diseases, sicknesses, or drug prescriptions you may have. If you meet all the entry criteria you will be scheduled for three more visits.

The second visit will require about one hour of your time. You will be asked to perform an exercise test on a treadmill to determine your ability to exercise. While walking on the treadmill you will be asked to exhale in a special tube so that oxygen and carbon dioxide levels can be measured. During the test you will be connected to a heart monitor and your blood pressure will be taken every two minutes. In addition a small sample of blood will be drawn from a vein in your arm before and after exercise for laboratory studies. You will perform this test at the Center for Exercise Science under the supervision of a physician. A physician will be present for each treadmill test at visits 2 and 3. Before the test you will have a brief physical examination, and a quality of life assessment. Then your body composition will be assessed using skinfold fat calipers. During this test a staff member will determine how much fat is on your body by pinching and measuring the thickness of your skin and underlying fat layer with the aid of a device called a caliper. Seven measurements will be taken at standard locations on your body.

After three days you will be asked to return for your third visit which will require about one and a half hours of your time. You will be asked to perform a walking test on the treadmill at two different levels of work. Each levels of work will range from easy to moderate. You will be asked to walk for three minutes at each workload (or until you start noticing discomfort). Between each work load you will be allowed to rest for 20 minutes. While walking on the treadmill, you will be asked to exhale in a special tube so that oxygen and carbon dioxide levels can be measured. In addition, during the last minute of each exercise bout you will be asked to breathe from a bag that contains a gas mixture. The gas mixture consists of 0.5% acetylene, 45% oxygen, and 10% helium in nitrogen. You will breathe from the bag for approximately eight seconds after which you will breathe normal room air. This procedure allows us to measure approximately how much blood the heart pumps. During the test you will be connected to a heart monitor (EKG) and your blood pressure will be taken every two minutes. In addition, a small

sample of blood will be drawn from a vein in your arm before and after exercise for laboratory studies.

The fourth visit will require about one hour and will not involve exercise. For visits 2 through 4, a venous catheter will be placed in your arm by qualified personnel. While you rest in a seated position, a 2 tablespoon blood sample will be taken. A low concentration of a dye (Evan's Blue, 1/4 tablespoon), which is used on a regular basis clinically, will be injected into the vein. At 10, 20, and 30 minutes following injection, a 1 tablespoon blood sample will be taken from the catheter. The Evan's Blue dye is used to determine the total amount of blood in your body.

6. Potential Health Risks or Discomforts

If you wish to discuss these or any other discomforts you may experience, you may call the Principal Investigator listed in #3 on this form.

Graded Exercise Test (GXT): The GXT is associated with a small risk of cardiovascular complications. The risk for exercise is about 3-4 non-fatal events in 10,000 GXT's, and one fatal event per 25,000 tests in a hospital population. The risk to you will be minimized in this study because all personnel involved are experienced in exercise testing and emergency treatment in readily available. Some fatigue and shortness of breath can be expected during testing. Following testing, you may experience some muscle soreness. This muscle soreness is normal and temporary and most likely will not interfere with your daily activities.

EKG (Electrocardiogram): No risks are involved.

Blood Draws: Placement of a venous catheter and drawing blood may involve some discomfort at the site, possible bruising and swelling around the site, rarely an infection, and uncommonly faintness from the procedure. Not more than eight tablespoons of blood will be taken. This is a small amount and should not cause fatigue or weakness.

Dye Injection: The dye which will be injected during visit four is non-toxic and does not have any drug action at the concentration used and therefore, should not cause any discomfort or illness.

Acetylene Rebreathing: There is no known risk associated with this procedure. The gas mixture used for the rebreathing study does not have an unpleasant odor or taste. The procedure is generally not uncomfortable in part due to the short exposure time (only 8 seconds) and a high concentration of oxygen (45%) in the bag. The most common complaint with the procedure is the weight of the rebreathing apparatus (bag and stopcock) on the mouthpiece. To avoid this problem, the rebreathing apparatus is supported by a pulley system attached to the ceiling. However, if you do not feel comfortable at any time during the procedure we will stop.

7. Potential Health Benefits to You or to Others

The major benefit to you for participating in this study is an evaluation of your cardiorespiratory fitness and body composition. Information regarding the relationship between your heart rate and the volume of blood pumped by your heart will also be available. Additionally, you will receive extensive testing of some of the hormones in your blood, the information from which may help your physician in treating your medical conditions.

8. Potential Financial Risks

There are no financial risks associated with your participation in this study.

9. Potential Financial Benefits to You or to Others

There are no financial benefits associated with your participation in this study except having the tests provided at no charge to you.

10. Compensation for Research Related Injury

In the unlikely event of you sustaining a physical or psychological injury which is caused by this study:

__X__ professional medical; or _____ prof. dental; or _____ prof. consultative

care at the J. Hillis Miller Health Center will be provided without charge. However, hospital expenses will have to be paid by you or your insurance provider. You will not have to pay hospital expenses if you are being treated at the Veterans Administration Medical Center (VAMC) and sustain any physical injury during participation in VAMC-approved studies.

11. Conflict of Interest

There is no conflict of interest involved with this study beyond the professional benefit from academic publication or presentation of the results. Your name and personal information will not appear in print or presented in a manner which could identify you.

12. Alternatives to Participating in this Research Study

You are free not to participate in this study. If you choose to participate, you are free to withdraw your consent and discontinue participation in this research study at any time without this decision affecting your medical care. If you have any questions regarding your rights as a subject, you may phone the Institutional Review Board (IRB) office at (352) 846-1494.

13. Withdrawal From this Research Study

If you wish to stop your participation in this research study for any reason, you should contact Matt Feigenbaum at (352) 392-9575. You may also contact the Institutional Review Board (IRB) office at (352) 846-1494.

14. Confidentiality

The University of Florida and the Veterans Administration Medical Center will protect the confidentiality of your records to the extent provided by law. The Study Sponsor, Food and Drug Administration, and the IRB have the legal right to review your records.

15. Assent Procedure (if applicable): Not applicable

APPENDIX D
INSTRUCTIONS FOR TESTING DAYS

To confirm or change appointment: Call 392-9575 and ask for Matt Feigenbaum.

Visit 2:
PHYSICAL EXAM, BODY COMPOSITION, HORMONE MEASUREMENTS, AND DIAGNOSTIC EXERCISE TEST (1.5 hours)

WHEN: Month _____

Day _____

Time _____

WHAT: During this visit you will be asked to perform an exercise test on a treadmill to determine your ability to exercise. While walking on the treadmill you will be asked to exhale in a special tube so that oxygen and carbon dioxide levels can be measured. During the test you will be connected to a heart monitor and your blood pressure will be taken every two minutes. In addition a small sample of blood will be drawn from a vein in your arm before and after exercise for laboratory studies. You will perform this test at the Center for Exercise Science under the supervision of a physician. A physician will be present for each treadmill test at visits 2 and 3. Before the test you will have a brief physical examination, and a quality of life assessment. Then your body composition will be assessed using skinfold fat calipers. During this test a staff member will determine how much fat is on your body by pinching and measuring the thickness of your skin and underlying fat layer with the aid of a device called a caliper. Seven measurements will be taken at standard locations on your body.

WHERE: The Center for Exercise Science
In the basement of the Florida Gymnasium

YOUR INSTRUCTIONS:

1) No meals, coffee, tea, or other beverage that contains caffeine 12 hours prior.

2) Wear a short sleeved shirt, T-shirt, or sleeveless shirt, comfortable walking shoes, and shorts or comfortable slacks. Ladies please do not wear body leotards or pantyhose.

3) No exercise 24 hours prior.

4) Take medications as you normally would.

To confirm or change appointment: Call 392-9575 and ask for Matt Feigenbaum.

Visit 3:
SUBMAXIMAL EXERCISE TEST -
CARDIAC OUTPUT AND HORMONE MEASUREMENTS
(2 hours)

WHEN: Month _____

Day _____

Time _____

WHAT: During this visit you will be asked to perform a walking test on the treadmill at two different levels of work. Each levels of work will range from easy to moderate. You will be asked to walk for three minutes at each workload (or until you start noticing discomfort). Between each work load you will be allowed to rest for 20 minutes. While walking on the treadmill, you will be asked to exhale in a special tube so that oxygen and carbon dioxide levels can be measured. In addition, during the last minute of each exercise bout you will be asked to breathe from a bag that contains a gas mixture. The gas mixture consists of 0.5% acetylene, 45% oxygen, and 10% helium in nitrogen. You will breathe from the bag for approximately eight seconds after which you will breathe normal room air. This procedure allows us to measure approximately how much blood the heart pumps. During the test you will be connected to a heart monitor (EKG) and your blood pressure will be taken every two minutes. In addition, a small sample of blood will be drawn from a vein in your arm before and after exercise for laboratory studies.

WHERE: The Center for Exercise Science
In the basement of the Florida Gymnasium

YOUR INSTRUCTIONS:

1) No meals, coffee, tea, or other beverage that contains caffeine 12 hours prior.

2) Wear a short sleeved shirt, T-shirt, or sleeveless shirt, comfortable walking shoes, and shorts or comfortable slacks. Ladies please do not wear body leotards or pantyhose.

3) No exercise 24 hours prior.

4) Take medications as you normally would.

To confirm or change appointment: Call 392-9575 and ask for Matt Feigenbaum.

Visit 4:
PLASMA VOLUME MEASUREMENT
(1 hour)

WHEN: Month _____

Day _____

Time _____

WHAT: During this visit a venous catheter will be placed in your arm by qualified personnel. While you rest in a supine position, a 2 tablespoon blood sample will be taken. A low concentration of a dye (Evan's Blue, 1/4 tablespoon), which is used on a regular basis clinically, will be injected into the vein. At 10 minutes following injection, a 1 tablespoon blood sample will be taken from the catheter. The Evan's Blue dye is used to determine the total amount of blood in your body.

WHERE: The Center for Exercise Science
In the basement of the Florida Gymnasium

YOUR INSTRUCTIONS:

1) No meals, coffee, tea, or other beverage that contains caffeine 12 hours prior.

2) Wear a short sleeved shirt, T-shirt, or sleeveless shirt, comfortable walking shoes, and shorts or comfortable slacks. Ladies please do not wear body leotards or pantyhose.

3) No exercise 24 hours prior.

4) Take medications as you normally would.

APPENDIX E
24 HOUR HISTORY QUESTIONNAIRE

24-HOUR HISTORY

NAME_____ DATE_____ TIME_____

How much sleep did you get last night? (Please circle one)

1 2 3 4 5 6 7 8 9 10 (Hours)

How much sleep do you normally get? (Please circle one)

1 2 3 4 5 6 7 8 9 10 (Hours)

How long has it been since your last meal or snack? (Please circle one)

1 2 3 4 5 6 7 8 9 10 11 12 (Hours)

List the meals or snack eaten:

When did you last have:

A cup of coffee or tea _____

Smoke a cigarette, cigar, or pipe _____

Drugs (including aspirin) _____

Alcohol _____

Last time donated blood _____

Any recent illness _____

Suffer from respiratory problem _____

What sort of physical exercise did you perform yesterday?

What sort of physical exercise have you performed today?

Describe your general feelings by checking one of the following:

_____ Excellent _____ Bad

_____ Very good _____ Very bad

_____ Good _____ Very, very bad

_____ Neither bad or good _____ Terrible

APPENDIX F
DATA COLLECTION FORMS

Investigator:	Site: Univ. of Florida	Protocol: BC

BODY COMPOSITION

Subject's Initials:	Subject's Code #:	Date Performed:

TEST	T1	T2	T3
Date:			
Skinfolds (SF)			
Chest			
Axilla			
Triceps			
Subscapula			
Abdomen			
Suprailiac			
Anterior Thigh			
Medial Gastroc			
SF Results			
% Fat			
Lean Body Mass			
Fat Weight			
Circumference			
Triceps Surii			
Height (cm)			
Weight (kg)			
TESTER			

Investig	Site:	Protocol:	Form:
	Univ. of Florida		SLGXT

GRADED EXERCISE TEST REPORT

Subject's Initials:	Subject's Code #:	Date

DUR min	SPD mph	GRADE %	HR B/min	BP mm/Hg	RPE	SAT %	COMMENTS
Sup							
Sit							
Std							
1	2	0					
2	2	0					
3	2	2					
4	2	2					
5	2	4					
6	2	4					
7	2	6					
8	2	6					
9	2	8					
10	2	8					
11	2	10					
12	2	10					
13	2	12					
14	2	12					
15	2	14					
16	2	14					
17	2	16					
18	2	16					
19	2	18					
20	2	18					
Max						Time:	

Investig.:	Site:	Protocol:	Form:
	Univ. of Florida		Recovery

GRADED EXERCISE TEST REPORT (Recovery)

Subject's Initials:	Subject's Code #:	Date :

DUR min	SPD mph	GRADE %	HR B/min	BP mm/Hg	RPE	SAT %	COMMENTS
IP							
1							
2							
3							
4							
5							
6							
7							
8							
9							
10							

Comments (Reason for Termination):

PLASMA VOLUME MEASUREMENT

Name: _____ Date: _____

Age: _____ Height (cm): _____ Weight: _____

Syringe Weight (grams)

Pre-injection _____

Post-injection _____

Volume injected (V) _____

Sample Volume (v), ml _____

Standard Dilution (D) _____

Standard Absorbance (St) _____

Sample Absorbance (T) _____

Hct, % _____

Plasma Volume, ml _____

Blood Volume, ml _____

Blood Volume, ml/kg _____

Red Cell Volume, ml _____

$$PV = \frac{(V \times D)(St \times v)}{1.03\ (T)}$$

where
- V = volume (ml) of T-1824 dye injected (22.6 mg/5ml)
- D = dilution of standard (1:250)
- St = absorbance of the standard
- v = volume of sample extracted (1.0ml)
- T = absorbance of plasma sample
- 1.03 = correction factor for dye uptake by tissues

Blood volume (BV) will be calculated as (PV)(100)/[100 - (0.91 x Hct)].
Red cell volume (CV) will be calculated as BV(Hct)/100.

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BIOGRAPHICAL SKETCH

Matthew S. Feigenbaum was born in Syracuse, New York, on October 9, 1966. He graduated from Seabreeze High School in Daytona Beach, Florida, in June, 1984.

In June 1988, he completed a Bachelor of Arts degree at Furman University in Greenville, South Carolina, with a major in health and exercise science. In June 1990, he completed the Master of Arts degree in education with a major in health and exercise science at Furman University.

In June 1990, he accepted a position as physical education teacher at Mainland High School in Daytona Beach, Florida. In September 1991, he founded the Personal Fitness Technology Program at Mainland High School, which was identified by the Florida Department of Education and the Centers for Disease Control and Prevention as a model program for promoting cardiovascular disease awareness and the use of technology in the physical education curriculum. He became the physical education department chair and coached football, soccer, and weight training.

In August 1993, he entered graduate school at the University of Florida to pursue the Doctor of Philosophy degree with a major in exercise and sports sciences and a minor in physiology. His degree program will be completed in 1997. Following graduation, he will pursue an academic career.

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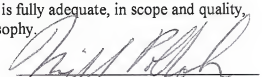

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Assistant Professor of Exercise and Sport Sciences

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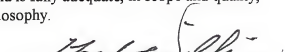

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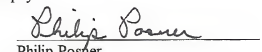

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This dissertation was submitted to the Graduate Faculty of the College of Health and Human Performance and to the Graduate School and was accepted as partial fulfillment of the requirements for the degree of Doctor of Philosophy.

May 1997

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